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American Heart Journal

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Original Communications

THE RELATION BETWEEN CIRCULATION TIME AND THE AMOUNT OF THE RESIDUAL BLOOD OF THE HEART

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THE introduction of determinations of circulation times has afforded the clinician assistance in diagnosis, prognosis, and management. A number of important studies have been published on this subject. Blumgart and Weiss[1] injected radium C intravenously and, with Geiger-Müller tubes, were able to determine the time when the injected substance arrived in different parts of the vascular system. The advantage of this method was that an objective determination of the time interval was obtained. Weiss was able to demonstrate a retardation, as compared with the normal, in patients with cardiovascular disease. In cases of cardiac insufficiency, it was observed that the protraction of the circulation time was, to a certain extent, proportional to the degree of insufficiency.

Winternitz and his co-workers[2] injected sodium aurodecholate into the vena cubiti and determined the time required for the patient to notice a bitter taste on his tongue. In spite of the fact that the patient's subjective cooperation is necessary, the inaccuracy of this method is surprisingly small, as results which were in very good agreement were obtained in repeated experiments on the same patient.

Employing Winternitz's method, Tarr, Oppenheimer, and Sager[3] found the normal circulation time to be 10 to 16 seconds with a mean value of 13 seconds, reckoning from the instant when the injection was given until the patient noticed the first taste sensation. For "compensated heart patients," Tarr found a moderate prolongation of the circulation time, and for the "decompensated patients" he found a considerable prolongation.

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Malmström and Nylin,[4] using decholin in 48 healthy persons, found that the first taste sensation appeared after 8 to 21 seconds; the mean value was 12 seconds. The sensation persisted for periods varying from 7 to 24 seconds, the mean being 12.8 seconds. The authors observed a decided relation between the circulation time and the size of the heart (measured in accordance with the method of Nylin, Lysholm, and co-workers[13]) in patients with compensated cardiovascular disease.

Nylin[5,6] earlier observed that the heart is subjected to considerable sudden volume changes both under physiologic and pathologic conditions and that these acute volume changes are due to variations in the amount of the residual blood. He pointed out also that the circulation time is not only dependent on the degree of insufficiency, but is also largely determined by the amount of the residual blood. He found, too, that the heart volume is considerably larger in the recumbent position than in an upright position, owing to the amount of the residual blood. Simultaneously with this change in heart volume, Malmström and Nylin[4] observed a prolongation of the circulation time in the recumbent position in comparison with that in the upright position.

Nylin[7-10] employed G. de Hevesy's method of labeling red blood corpuscles and applied this method to the problem of the circulation time and the amount of the residual blood. These investigations show that, however subjective the method may be, the decholin method agrees on the whole with the objective method in which labeled red blood corpuscles are used.

In the present study a more thorough investigation has been made of the prolongation of the circulation time in the dilated heart due to the increased amount of residual blood. In particular, the connection between the circulation time and the heart volume has been studied, and the results have been handled statistically.

The studies of Nylin and his co-workers have proved clearly that, above all, the circulation time depends on the amount of the residual blood in the heart, and only to a slight extent on the degree of decompensation, i.e., of congestion. This relationship has not been pointed out previously. The establishment of this connection between circulation time and the amount of the residual blood is not only of theoretical but also of important practical interest. Thus, it is necessary to pay due attention to the varying amounts of residual blood in determinations of the blood volume, and perhaps also in other investigations of the blood flow.

The determination of the circulation time affords a possible method of determining in a simple way whether or not the heart is dilated.

METHOD

Determinations of the circulation time and venous pressure were made on patients under resting conditions. The patient, the upper part of whose body was bare, lay flat on his back on a bed from which the pillows had been removed. A cannula with an inside diameter of 0.9 mm. was inserted into a cubital vein. The cannula, which was heparinized, was connected with a fitting, in which an

upright manometer tube was fixed. The measurement of the venous pressure was made when the injection needle was on a level with the central axillary line. By means of slight pressure with the hand around the patient's arm above the cannula one could easily make sure whether the venous pressure rose when the arm was compressed and fell when the pressure was relaxed, and that there was a free connection. Into the fitting, which was constructed as a three-way tap, an injection syringe could be connected. By turning the three-way tap, the injection syringe could be connected to the cannula.

In determinations of circulation times, 5 ml. of a 20 per cent decholin solution was injected as quickly as possible. The time was taken from the instant the syringe plunger reached the bottom. The patient then had to indicate when he first perceived the sensation of a bitter taste, when it began to recede, and when it had disappeared entirely.

The method has been previously described in detail and critically discussed by Malmström and Nylin.[4]

The determinations of the heart volume were made in accordance with the method worked out by Lysholm, Nylin, and co-workers.[12,13] In healthy persons, according to these authors, the normal mean value of the absolute heart volume (V) is 700 c.c. with a range of 457 to 945 cubic centimeters. The relative heart volume ($V/M.^2$), i.e., the volume expressed in cubic centimeters per square meter of body surface, is, on the average, 370 c.c. with a range of 250 to 490 cubic centimeters.

PRESENT INVESTIGATIONS

The material, which comprised 308 patients with heart disease, was divided into "compensated" and "decompensated" cases. The presence of decompensation was determined by general signs of congestion, such as palpable liver, palpable spleen, edema, roentgenologically demonstrable lung congestion. Roentgenologic determinations of the heart volume, determinations of the circulation time, and measurements of the venous pressure were made on every patient.

Table I is a summary of the material, with calculations of the mean, standard error of the mean, standard deviation, and coefficient of variation.

There is a clear correlation between both the absolute (V) and the relative ($V/M.^2$) heart volume and the circulation time, with a correlation coefficient of 0.51 and 0.50, respectively (Table II and Fig. 1). There does not appear to be any definite connection between the heart volume or heart volume per square meter of body surface and the venous pressure, as appears from the low correlation coefficients shown in Table II. From Fig. 2 it is clear that, when the heart volume increases from 350 to 900 c.c. per square meter of body surface in the compensated cases, the rise in venous pressure is extremely slight. Consequently, the conclusion may be drawn that the circulation time is determined chiefly by the heart volume, and therefore by the amount of the residual blood, and to a lesser degree by the height of the venous pressure in the case of compensated heart disease. If a comparison is made of the relation between the absolute heart volume

TABLE I. THE HEART VOLUME, HEART VOLUME PER SQUARE METER OF BODY SURFACE, VENOUS PRESSURE, AND CIRCULATION TIME IN CASES OF COMPENSATED AND DECOMPENSATED HEART DISEASE

	NUMBER	M	$\pm \sigma_m$	S. D.	$V = \frac{100 \text{ S.D.}}{M}$
Compensated:					
Heart volume in cubic centimeters (V)	214	987.6	±23.3	±340.3	34.5
Heart volume in relation to the estimated body surface ($V/M.^2$)	202	568.7	±13.9	±197.3	34.7
Circulation time in seconds (first taste sensation)	214	18.68	± 0.53	± 7.68	41.1
Venous pressure in centimeters	213	8.97	± 0.23	± 3.39	37.8
Decompensated:					
Heart volume in cubic centimeters (V)	94	1,437.2	±55.3	±536.3	37.4
Heart volume in relation to the estimated body surface ($V/M.^2$)	93	832.5	±32.8	±316.3	38.0
Circulation time in seconds (first taste sensation)	94	27.68	± 1.27	± 12.30	43.4
Venous pressure in centimeters	94	18.10	± 0.65	± 6.32	35.0

TABLE II. THE RELATION BETWEEN THE HEART VOLUME IN CUBIC CENTIMETERS AND THE CIRCULATION TIME (THE FIRST TASTE SENSATION) IN SECONDS AND BETWEEN THE HEART VOLUME AND THE VENOUS PRESSURE IN CENTIMETERS IN CASES OF COMPENSATED HEART DISEASE

CORRELATION	NUMBER	$r \pm \sigma_r$
Compensated:		
Volume (V)—circulation time	214	0.51 ± 0.051
Volume (V)—venous pressure	213	0.16 ± 0.067
Volume ($V/M.^2$)—circulation time	202	0.50 ± 0.053
Volume ($V/M.^2$)—venous pressure	201	0.15 ± 0.069
Circulation time—venous pressure	213	0.18 ± 0.066

and the time from the moment of the injection to the last taste sensation instead of, as before, to the first taste sensation, a correlation coefficient of 0.40 is found (Table III), which indicates that here, too, there is a relation between the amount of the residual blood and the length of the circulation time (determined by the cessation of the taste sensation) in the compensated cases.

TABLE III. THE RELATION BETWEEN THE ABSOLUTE HEART VOLUME AND THE CIRCULATION TIME* AND BETWEEN THE ABSOLUTE HEART VOLUME AND THE DURATION OF THE TASTE SENSATION†

CORRELATION	NUMBER	$r \pm \sigma_r$
Heart volume (V)—circulation time (last value)	198	+0.40 ± 0.060
Heart volume (V)—difference in circulation time	198	+0.27 ± 0.066

*The time from the moment of the injection to the disappearance of the bitter taste.
†The time between the first and last taste sensations.

If the time interval between the first and last taste sensation is calculated and correlated with the heart volume, a correlation coefficient of only 0.27 is obtained. From these investigations it appears that, for judging the relation between the magnitude of the heart volume (and with it the amount of the residual blood) and the circulation time, the first taste sensation is the better guide.

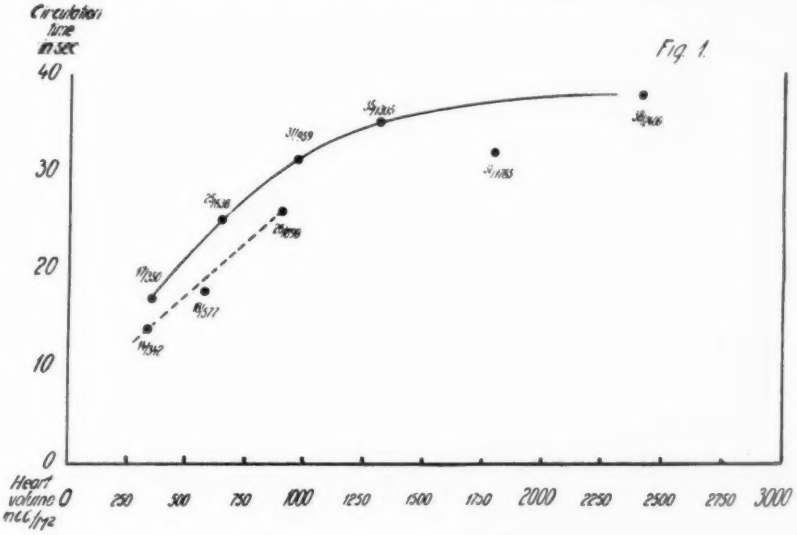
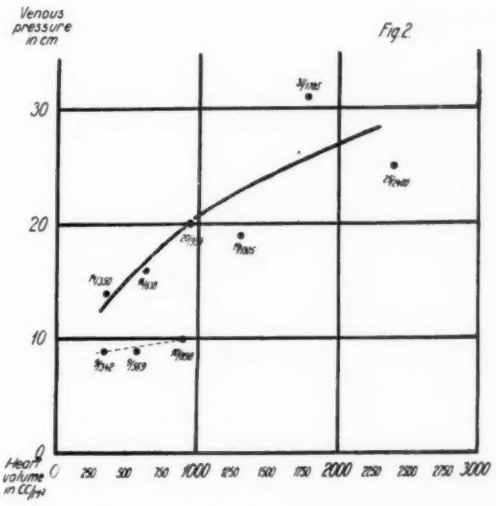


Fig. 1.—The relation between the relative heart volume (V/M.²) and the circulation time in patients with compensated and decompensated heart disease is shown. The patients were divided into groups according to the heart volume, and each figure represents the mean figure for the values falling within a class interval of 400 cubic centimeters. The chart was compiled from 202 cases of compensated and 93 cases of decompensated heart disease.



g. 2.—The relation between the relative heart volume (V/M.²) and the venous pressure in cases of compensated and decompensated heart disease. The class divis'on of the patients is the same as that used in Fig. 1.

In the decompensated heart cases, there is a clear correlation between both the absolute (V) and the relative ($V/M.^2$) heart volume and the circulation time, although it is less pronounced than in the compensated cases. The correlation coefficients are 0.45 and 0.37 (Table IV and Fig. 1). This correlation is, however, greater in reality than appears from the correlation coefficient, as the line which represents the correlation is curved (Fig. 1).

TABLE IV. THE RELATION BETWEEN THE HEART VOLUME IN CUBIC CENTIMETERS AND THE CIRCULATION TIME (FIRST TASTE SENSATION) IN SECONDS, AND BETWEEN THE HEART VOLUME AND VENOUS PRESSURE IN CASES OF DECOMPENSATED HEART DISEASE

CORRELATION	NUMBER	$r \pm \sigma_r$
Decompensated:		
Volume, rtg.* (V)—circulation time	94	0.45 ± 0.082
Volume, rtg. (V)—venous pressure	94	0.36 ± 0.090
Volume, rtg. ($V/M.^2$)—circulation time	93	0.37 ± 0.090
Volume, rtg. ($V/M.^2$)—venous pressure	93	0.37 ± 0.090
Circulation time—venous pressure	94	0.39 ± 0.088

*Rtg.=roentgenologic.

In comparison with cases of compensated heart disease, there is in cases of decompensated heart disease a closer relation between the heart volume and the venous pressure, as appears from the relatively high correlation coefficient of 0.37 (Table IV and Fig. 2).

TABLE V. THE CORRELATION BETWEEN THE ABSOLUTE HEART VOLUME AHD THE CIRCULATION TIME* AND BETWEEN THE ABSOLUTE HEART VOLUME AND THE DURATION OF THE TASTE SENSATION†

CORRELATION	NUMBER	$r \pm \sigma_r$
Decompensated:		
Volume (V)—circulation time (last value)	78	+0.42 ± 0.093
Volume (V)—difference in circulation time	78	+0.21 ± 0.108

*The time from the moment of injection to the disappearance of the bitter taste.
†The time between the first and last taste sensations in cases of decompensated heart disease.

As in the compensated cases, there is also in the decompensated cases an obvious correlation between the absolute heart volume and the time interval between the moment of injection and the last taste sensation, with a correlation coefficient of 0.42 (Table V). The duration of the taste sensation only gives a correlation coefficient of 0.21.

SUMMARY

A statistical investigation on a considerable number of patients with both compensated and decompensated heart disease as to the relation between the size of the heart, the heart volume determined roentgenologically, and the circulation time gives the following results:

In both compensated and decompensated heart disease there is a statistically verified correlation between the heart volume, i.e., the amount of the residual blood, and the circulation time (first taste sensation). There is a similar correlation between the heart volume and the circulation time (the last taste sensation). The explanation of these two circumstances, which were first observed by Nylin, is found if it is assumed that the greater the amount of the residual blood in the heart the longer time it takes for the test substance injected to become mixed with the residual blood and to reach the peripheral arterial system. Similarly, the late disappearance of the bitter taste is explained by the fact that it takes longer for the heart to pump out the test substance when the amount of the residual blood is large, as in cases of dilated hearts.

These statistical results are in complete accord with Nylin's experiences in determining the circulation times by means of radioactive phosphorus.

The authors wish to express their gratitude to Professor G. Dahlberg of the Race Biological Institute at Upsala for his kind assistance with the statistical studies.

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THE HEART IN PRIMARY SYSTEMIC AMYLOIDOSIS

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THERE is a large group of uncommon diseases, some systemic in nature, in which involvement of the heart may lead to cardiac failure.[38] Few of these[39,40] have been so delineated that their clinical, laboratory, and pathologic sequences differentiate them easily from the more common types of cardiac disease. By observation of certain peculiarities of their manifestations, and by the recognition of the basic process or lesions in other tissues, one is not likely to overlook the significance of certain of these generalized diseases which may be accompanied by cardiac signs and symptoms.

Amyloidosis, particularly the primary systemic form of the disease, constitutes one member of this group of miscellaneous, obscure cardiac diseases. Weiss and co-workers[40] have pointed out that an accurate etiologic classification of these rare types of disease is mandatory, mainly because of the practical importance of specific therapy. While no patients with primary amyloidosis have recovered, none has received a form of therapy which appears to be efficacious in the secondary type of amyloidosis.[41-67]

The purpose of the present report is (1) to summarize the clinical and pathologic data available in the published reports of over forty cases of primary systemic amyloidosis from the standpoint of clinical cardiac and systemic manifestations, aids in diagnosis, electrocardiographic records, and pathologic changes in cardiac tissues; and (2) to record an additional case of primary amyloidosis in which extensive, diffuse, myocardial, amyloid infiltration was responsible for progressive cardiac failure and death.

CASE REPORT

First Admission.—A. S., —U47646, a married white woman, 59 years of age, the wife of a clergyman, first entered the hospital on July 6, 1939.

Clinical History: For six months before entry she had noted increasing exertional dyspnea and weakness. Three months before, edema of the ankles occurring at the end of the day appeared. Three days before, she had first noticed substernal pain following moderate exertion. An electrocardiogram, done four months before entry, showed a very low voltage and a moderate left-axis deviation. Family and past history contained several significant items. Her father died at the age of 72 years of peptic ulcer. Her mother's death at the age of 75 years was due to a cerebrovascular accident. The patient had two spontaneous abortions at two and three months. The first was followed by an attack of "rheumatism," which was relieved by uterine curettage.

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Migraine headaches, precipitated by the ingestion of eggs, had occurred since childhood. Her three children had similar headaches. One year before, mild enlargement and pain in the knees and small joints of the hands occurred. These articular symptoms had persisted but were stationary.

Physical Examination: The patient was an asthenic, well-nourished white woman. The temperature was 37.4°C.; pulse rate, 90; respiratory rate, 24; weight, 53.6 kilograms (118 pounds). The head, eyes, ears, nose, and mouth were normal. When she was in the sitting position, the cervical veins were distended to a point 12 cm. above the second interspace. The left border of the heart was 1.5 cm. to the left of the mid-clavicular line. There was no enlargement to the right. A soft systolic murmur of moderate intensity could be heard at the mitral and aortic areas. The aortic second sound was hollow. There were occasional ventricular extrasystoles. The blood pressure was 95/60. The lungs were clear throughout. Examination of the abdomen, back, rectum, genitals, and nervous system showed nothing abnormal. There were obvious varicose veins and slight pitting edema of both lower extremities. The interphalangeal joints of both hands were slightly widened, without any limitation of motion. Fluoroscopy of the chest showed a diffuse enlargement of the heart, involving mainly the left ventricle and auricle. The right side of the heart was enlarged to a lesser extent. The cardiac contractions were poor, and, at the apex of the left ventricle, were almost absent. The bronchovascular markings near the hilum of each lung were widened.

Laboratory Examination: Examination of the blood gave the following data: hemoglobin, 85 per cent (12.3 Gm.); red blood cells, 4.5 million; white blood cells, 10,100, polymorphonuclear leucocytes, 58.5 per cent (filamented, 48.5 per cent; nonfilamented, 10 per cent); eosinophiles, 2 per cent; basophiles, 0.5 per cent, lymphocytes, 32 per cent, monocytes, 7 per cent. The erythrocytes and platelets were normal. The sedimentation rate (Wintrobe) was 17 mm. (cell volume, 44 c.c. per cent; corrected rate, 20 mm.). Blood serum proteins: albumin, 3.61 per cent; globulin, 1.90 per cent; albumin-globulin ratio, 1.9. The urine contained a slight trace of albumin. Tests for urobilin and urobilinogen were positive in undiluted urine but were negative in dilutions of 1:20. No serologic tests for syphilis were done.

Gastric analysis with histamine showed a level of free hydrochloric acid reaching 48 degrees, with the total acidity reaching 64 degrees. Pepsin and rennin were present in the gastric juice. The basal metabolic rate was −4 per cent.

A clinical diagnosis of congestive cardiac failure due to coronary arteriosclerosis was made. The patient's course was uneventful. She was advised to continue at home a regime of bed rests, Galen B (the vitamin B complex from rice polishings), a high protein diet, and digitalis.

Second Admission.—The patient's second entry was on August 17, 1939. One week before admission an acute upper respiratory infection with pain in the legs and back occurred. Shortly thereafter she developed pain in the right lower chest, accentuated by respiratory movements. Increasing dyspnea, palpitation, and slight cough and a temperature of 38.8°C. appeared. There was a slight increase in peripheral edema. These symptoms and findings were less severe at the time of entry into the hospital.

On admission, physical signs of a right pleural effusion were found, and 500 c.c. of serosanguineous fluid were removed from the right pleural cavity. Its specific gravity was 1.016 and the Rivalta test was positive. No bacteria were present, and the sediment contained only mesothelial and red and white blood cells. The heart was still enlarged. The heart sounds were the same as on previous examination. The cardiac rhythm was regular; the rate was 90.

Laboratory Examination: Examination of the blood gave the following data: hemoglobin, 86 per cent (12.5 Gm.); erythrocytes, 4.25 million; leucocytes, 9,900; polymorphonuclear leucocytes, 55.5 per cent (filamented, 47.5 per cent; nonfilamented, 8 per cent); eosinophiles, 3 per cent; basophiles, 0; lymphocytes, 31.5 per cent; monocytes, 10 per cent. The erythrocytes and platelets were normal. Observed sedimentation rate, 37 mm. (cell volume, 41 c.c. per cent; corrected rate, 34 mm.). The urine contained a moderate amount of albumin. Tests for urobilin and urobilinogen were positive in an undiluted specimen but were negative at 1:20 dilution. Blood serum proteins: total, 6.4 mg. per cent; albumin, 4.08 mg. per cent; globulin, 2.32 mg. per cent;

albumin-globulin ratio, 1.76. An electrocardiogram showed a rate of 93, ventricular premature systoles, slight left-axis deviation, low-voltage QRS complexes, and low T waves in Leads I and II (Fig. 1).

During the next twenty-six days, the amount of fluid in the right pleural cavity continued to decrease. The sedimentation rate dropped to 27 mm. Despite almost complete bed rest and a maintenance dose of digitalis of 1 dg. per day, the cardiac rate remained at about 90. Four intravenous mercurial injections produced a good diuresis and prevented a gain in weight. The intake of fluids and salt was restricted.

Third Admission.—The last entry in the hospital was on Nov. 13, 1939. While at home, the patient had not improved and had been bedridden. Six days before admission, the dyspnea had increased. She had noted a constricting sensation in the thorax, with severe inspiratory, bilateral thoracic pain. She became orthopneic and developed a low-grade fever. Four days before admission, she became nauseated and began to vomit. Swelling of the face had been present for some time but was more pronounced shortly before entering the hospital.

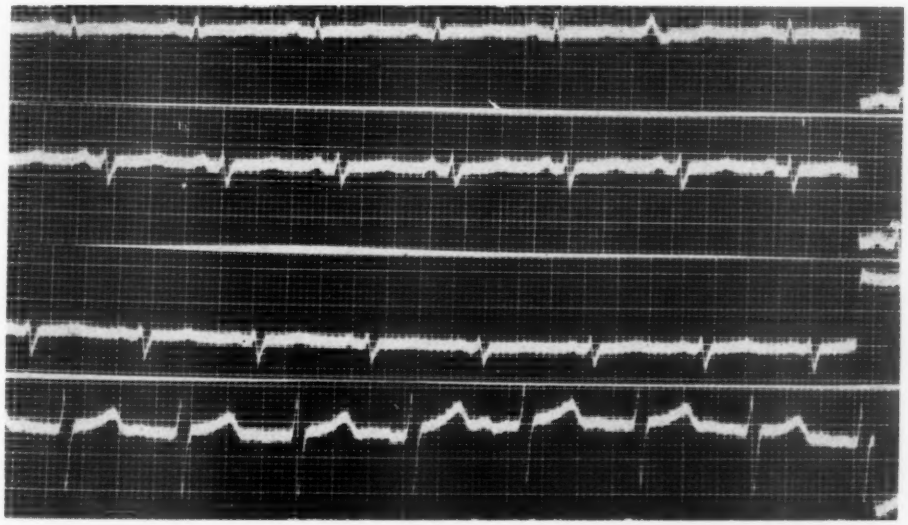

Fig. 1.—Electrocardiogram made on Aug. 1, 1939.

Physical Examination: The temperature was 38° C.; pulse rate, 90; respiratory rate, 26. The patient was orthopneic and slightly cyanotic. There was edema of the face and ankles. Abnormal venous distention of the neck was noted. The chest expanded poorly and there were physical signs of fluid in both pleural cavities. The heart was enlarged to the left in the fifth intercostal space. The sounds were poor. A gallop rhythm was heared at the apex, and a systolic murmur was heard at the oartic area. The blood pressure was 90/75. There was guarding in the upper right quadrant of the abdomen and the liver was enlarged. Edema of the ankles and sacral region was present.

Laboratory Examination: Examination of the blood gave the following data: hemoglobin, 88 per cent (12.8 Gm.); red blood cells, 4.62 million; white blood cells, 12,600; polymorphonuclear leucocytes, 65 per cent; lymphocytes, 25 per cent; monocytes, 10 per cent. The erythrocytes and platelets were normal. The feces were normal. An electrocardiogram showed a rate of 100 per minute, low voltage of the QRS complex, left-axis deviation, low T_1, T_2, T_3, and T_4, slight elevations of S-T_4, and a small R_4.

Course: Removal of 700 c.c. of fluid from the right pleural cavity produced little change in the patient's condition which remained poor during the next two weeks. She had frequent attacks of migraine with nausea and abdominal distention. The heart sounds had a poor quality; there was a gallop rhythm with occasional ventribular extrasystoles. The rate continued at 100. The cervical veins were distended and pulsating, and hepatic enlargement was progressing. Bilateral hydrothorax and edema of the face and legs were not relieved by mercurial injections and aminophylline. During this period, lumbar puncture showed clear cerebrospinal fluid, containing eight lymphocytes per cubic millimeter. The initial pressure was 180 mm. of water, and the Pandy, Lange, and Kahn tests gave normal findings.

On Nov. 30, 1939, the patient became stuporous and was found to have a left flaccid hemiplegia. Within the next few days the deep reflexes on the left side returned and she became more responsive. During the following three weeks, the muscular tone and voluntary movements on the left side increased, though she remained confused and disoriented, and had considerable difficulty in speech.

The cardiac status slowly became worse. Pulmonary congestion became more pronounced. The pulse rate varied between 110 and 130, and the respiratory rate, between 25 and 35. Several episodes of Cheyne-Stokes breathing responded to amonophylline. During the last three weeks of life, there was a gradual elevation of temperature to a terminal level of 40.4° C. The edema of the arms and legs was much more pronounced on the left hemiplegic side of the body for two days before death. This difference had no relation to position in bed. Death from cardiac failure occurred on Jan. 11, 1940, approximately one year following the onset of cardiac symptoms.

Autopsy Report.—The autopsy (UA 40.5) was performed one and one-half hours after death. There was marked wasting of the subcutaneous fat and musculature. The temporal and cervical veins were distended and tortuous. The abdomen was distended. There was edema of both legs and arms, greater on the left side. The inter-phalangeal joints of the hands were slighty enlarged. The surface of the skin, the eyes, ears, nose, and mouth were normal.

The peritoneal cavity and each pleural cavity contained 1,000 c.c. of clear yellow fluid. The heart was enlarged. The left border extended 11 cm. to the left of the midline and the right border 5 cm. to the right of the midline. Dense bilateral pleural fibrous adhesions were present. The heart weighed 500 Gm. The serosal surfaces were smooth and glistening and had normally distributed pericardial fat. All of the cardiac chambers were moderately dilated. There was anatomic patency of the foramen ovale. The ventricular walls were hypertrophied, with the left averaging 2.3 cm. in thickness and the right, 1.3 cm. in thickness. The auricular walls varied between 0.2 and 0.6 cm. in thickness. All portions of the myocardium were unusually firm and stiff; the auricular walls had a leathery consistency. There was a pale brownish-tan pallor of the entire myocardium. Throughout this layer, including the interventricular septum, trabeculae carneae, and ventricular papillary muscles, was a diffuse network of pale grayish-yellow, translucent material, tending to be concentrated about visible blood vessels and within the interstitial tissues. Strong solution of iodine (U. S. P.) stained the myocardium diffusely, producing a mahogany-brown color, with the translucent areas taking the stain more deeply (Fig. 2). The amyloid infiltration was most abundant in the left ventricular wall. Less abundant infiltration had occurred in the epicardial fat. The cardiac valves were not grossly altered. There was a mild translucent intimal thickening of the main coronary arteries, but these vessels had widely patent lumens, and no atheromatous lesions were present. No nodular amyloid deposits were encountered in the heart. Both auricular appendages contained adherent ante-mortem thrombi.

The right lung weighed 300 grams and the left lung weighed 340 grams. Both lungs were partially atelectatic and mildly congested and edematous. The cut surfaces had a pale, pink, glistening, moist appearance, and a rubbery consistency.

The liver weighed 1,080 grams. Its parenchyma was brown in color, and there was moderate central lobular congestion. A 1 cm. cavernous hemangioma lay beneath the capsular surface of the right lobe. The gall bladder was distended with bile, but its wall was normal. The spleen weighed 70 grams and its capsule was smooth. The splenic pulp was firm, dark purple in color, and was not hyperplastic. Scattered throughout were small 1 to 2 mm. zones of translucent, soft, amyloid material. The pulp stained diffusely with strong solution of iodine (U. S. P.). The discrete amyloid masses stained a deeper brown.

Except for loss of distinct corticomedullary differentiation, the kidneys were normal. The pancreas and adrenal glands were grossly normal.

The ovaries, Fallopian tubes, and uterus were atrophic. The uterine canal was lined by a thin, pale, smooth endometrial layer. There was an unusual glistening pallor and translucency of the inner half of the myometrial layer.

Fig. 2.—Section of heart showing diffuse amyloid infiltration of myocardium and less abundant deposition in the epicardium and endocardium (× 4/5). Stained with strong solution of iodine (U. S. P.) followed by acidified Eastman x-ray fixer. Photographed with red Wratten B filter No. 25.

Almost the entire muscular layer of the stomach, especially of the pyloric end, was thickened, firm, and rubbery. Extensive deposits of pale yellowish-gray, translucent amyloid material lay between isolated muscle bundles. This muscular alteration was particularly marked in and just above the pyloric sphincter. On the surface, the amyloid deposits appeared as longitudinal ridges and cords, visible through the transparent serosal layer. There was no gross evidence of amyloid infiltration of the large and small bowel, but the outer muscular layer of the lower esophagus showed changes similar to those seen in the stomach. After fixation for several days in a solution of formaldehyde (U. S. P.), the gastroentric amyloid took on a brownish-purple color but retained its shining, translucent characteristics. The cardiac amyloid did not show this alteration.

The bone marrow of the lumbar spine was normal. A few small atheromatous plaques were present in the intima of the aorta. There was no gross alteration of the superior or inferior vena cava.

The entire right frontal lobe of the brain was pale, flattened, and soft. On section, this frontal lobe, with the underlying basal nuclei, was almost entirely liquified. The superficial layer of the cortex was relatively intact. The right anterior and right middle cerebral arteries

and the left carotid artery were occluded by ante-mortem thrombi. The pituitary and thyroid glands were normal.

Microscopic Description: The walls of both ventricles of the heart had a similar histologic appearance. Many of the fat cells of the subendocardial layer had thickened eosinophilic cell membranes, which gave positive staining reactions for amyloid. All layers of the main coronary arteries and the medium-sized arteries and veins in this layer were moderately infiltrated with homogeneous eosinophilic amyloid material.

There was diffuse intercellular amyloid deposition in the myocardium (Fig. 3). The material lay between individual muscular cells and was continuous with amyloid infiltrating the adventitia of blood vessels and that surrounding the endothelial wall of small capillaries. When seen in cross section, each myocardial fiber was encased in an amyloid ring, producing a honeycomb appearance. The amount of intercellular amyloid varied in different parts of the myocardium. Where it was most abundant, the enclosed myocardial fibers were compressed, atrophied, granular, and degenerating. The nuclei were distorted. Some fibers had disappeared, leaving fusiform spaces in the amyloid matrix. Other fibers were absent, leaving amyloid rings which occasionally contained small clumps of eosinophilic debris and golden-brown pigment. Some areas showed large amyloid sheets with no residual myocardial fibers. Elsewhere in the interstitial tissue were nodular, small, rounded amyloid deposits. Small lipid globules in many of the degenerating muscle cells were revealed with the sudan IV stain. For the most part, the interstitial amyloid was homogeneous, compact, refractile; in some areas it was frayed and fibrillary. The amyloid rings had largely replaced the pericellular reticulum fibers. By combining the Laidlaw connective tissue and Congo red stains, it was noted that the remaining reticulum fibers usually lay between the myocardial cell membrane and the pericellular amyloid ring. No cellular reaction to the amyloid had occurred, and there was no acute myocardial necrosis or fibrosis. There was a greater degree of amyloid infiltration in the left ventricle as compared to the right. All the myocardial blood vessels, particularly the arteries, contained rounded, confluent amyloid deposits, which centered in the medial layer with extension into the adventitia (Fig. 4). A few atrophic nuclei of the smooth muscle cells remained. None of the cardiac vessels had significantly narrowed lumens. The interstitial, pericellular, and vascular amyloid distribution in each auricle was similar to that seen in the ventricles. In addition, there were extensive, rounded, irregular confluent amyloid masses in both the endocardial and pericardial layers. The auricular appendages contained organizing thrombi.

All the cardiac valves had a similar histologic appearance. The valvular endothelium was intact. Few connective tissue nuclei remained. The connective tissue fibers had lost their fibrillary character and had become swollen, eosinophilic, and amorphous. In all valves were small, irregularly rounded, centrally placed amyloid nodules.

Small amyloid deposits were noted in the media and the intima of the pulmonary artery. The media of almost all of the medium-sized pulmonary arteries and veins contained amyloid material. Less abundant deposits were present in the alveolar walls and in the submucosa of the bronchioles. The alveoli were atelectatic and many were lined by large, cuboidal epithelial cells. The aveolar walls showed a fibrous thickening in addition to that caused by the amyloid infiltration. Many macrophages and fewer red and white blood cells lay in the alveolar spaces.

There was moderate central sinusoidal congestion of the hepatic lobules, but the parenchymal cells were not altered. Large amyloid deposits were present in the fibrous septa of the cavernous hemangioma. Interstitial infiltration of all the layers of the gall bladder had occurred. The media of the arteries was similarly involved.

The Malpighian bodies and much of the splenic pulp had been replaced by amyloid material. Little was present in the walls of the central arteries. In the pulp, the material lay between the sinusoids, adjacent to the reticulo-endothelial cells lining the vascular channels.

There was no alteration of the pancreatic parenchyma. The media of some of the medium-sized arteries contained amyloid deposits.

An occasional renal glomerular tuft was distended with amyloid material. The convoluted tubules were dilated and many contained albumin and desquamated epithelial cells.

A diffuse amyloid infiltration of the connective tissue of the myometrium and endometrium was noted (Fig. 5). The amyloid material in the uterus was more pale and fibrillary than else-

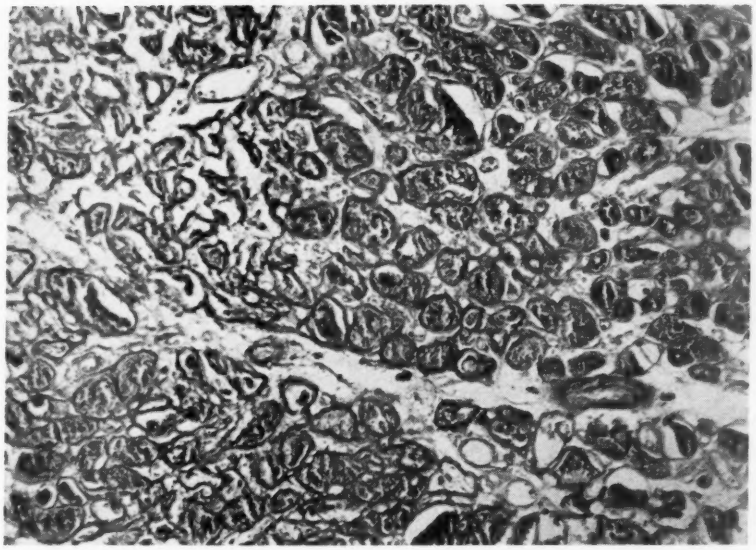

Fig. 3.—Myocardium showing pericellular amyloid rings, with atrophy or absence of muscle fibers. (× 120). Crystal violet stain.

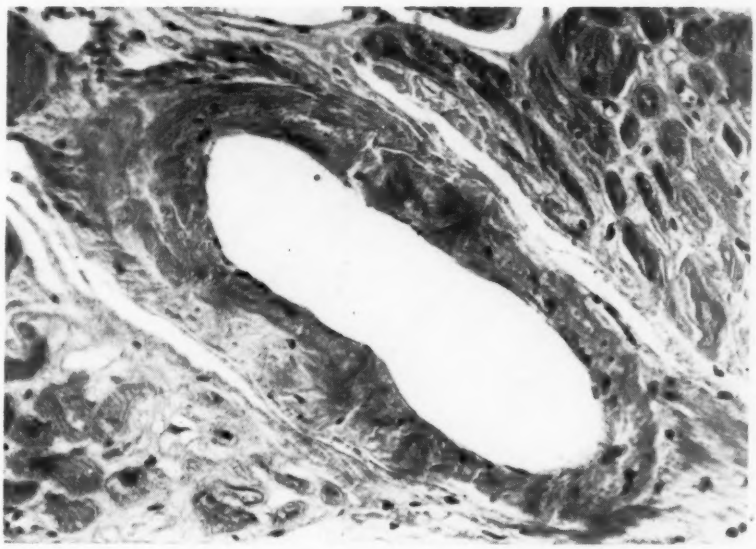

Fig. 4.—Myocardial vein with amyloid infiltration of its wall (× 250). Hematoxylin and eosin stain.

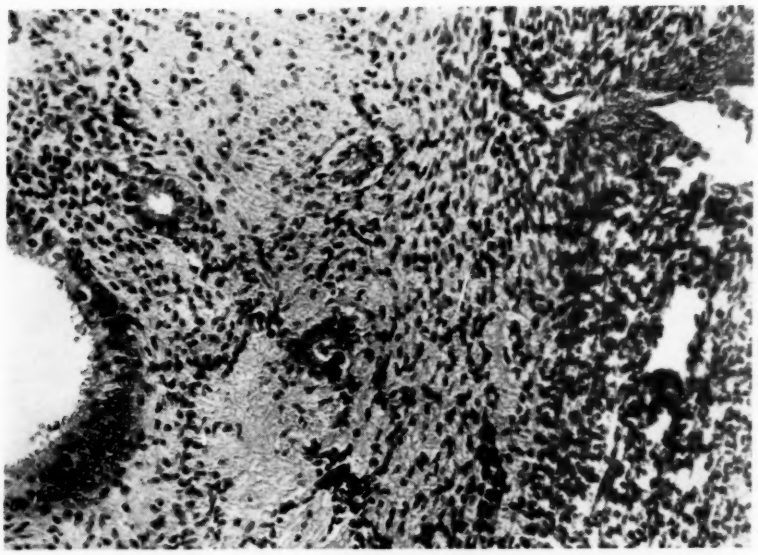

Fig. 5.—Endometrium showing interstitial amyloid infiltration (× 200). Hematoxylin and eosin stain.

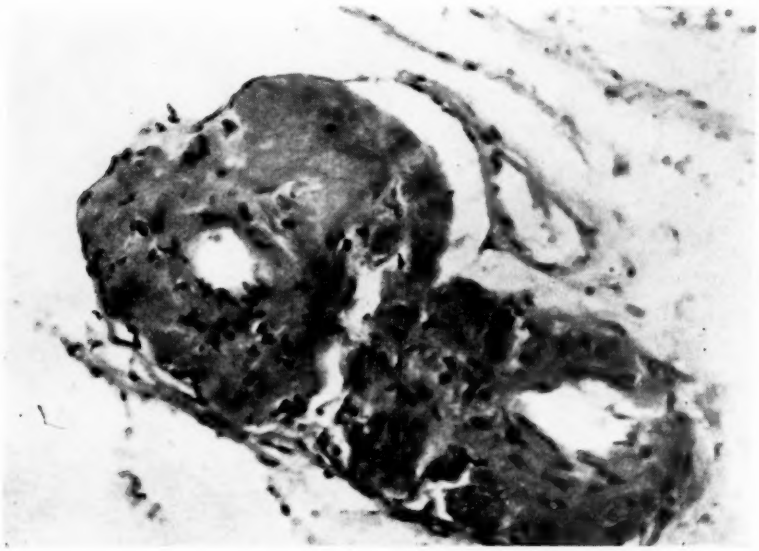

Fig. 6.—Small arteries of adrenal capsule showing extensive amyloid infiltration (× 250). Hematoxylin and eosin stain.

where. The media of the small and medium-sized arteries in the uterine wall contained amyloid masses.

Similar interstitial and vascular masses of amyloid were present in the ovary and cervix. Minimal infiltration of the submucosa of the Fallopian tubes had occurred.

Amyloid deposition in the gastroenteric tract, including the esophagus, stomach, small bowel, and colon, had an unusual distribution. While the normal outlines of the muscular bundles remained, considerable atrophy or complete disappearance of many of the smooth muscle cells had occurred. This muscular alteration was due to compression by narrow fusiform or ovoid intercellular amyloid masses. Less abundant interstitial amyloid was present in the submucosa. Bulky deposits were encountered in both the arteries and veins of the gastroenteric tract.

Almost identical muscular, vascular, and submucosal deposits of amyloid were present in the urinary bladder.

The aortic intima was widened and was composed largely of hyalinized collagen. Small groups of lipid-containing macrophages were noted. Both the intimal and medial layers contained small interstitial amyloid deposits. There was interstitial amyloid infiltration of the media of the inferior vena cava. The bone marrow of the lumbar spine contained fat cells and hemopoietic tissue in normal proportions. Erythrocytic, myelocytic, and megakaryocytic elements were present in the usual numbers. Several small irregular amyloid deposits were noted. No plasma cells were identified.

The pituitary gland was not significantly altered. The acini of the thyroid gland were larger than normal and were distended with colloid substance. The cortical layer of the adrenal glands was moderately hyperplastic and the cortical cells were well supplied with lipid material. Minimal interstitial amyloid deposits were present in this layer. The medial layer of both the adrenal and periadrenal arteries and veins contained masses of amyloid substance (Fig. 6).

The left internal carotid artery had a thin wall. The intima and much of the media were the site of extensive atherosclerosis with calcification. The lumen contained a nonorganizing thrombus. The internal elastic membrane had been partially destroyed. Small amyloid deposits were noted in the media.

The lumens of both the right anterior and middle cerebral arteries were occluded by thrombi. That of the former had undergone early organization while the thrombus in the latter vessel was completely organized and recanalized. Amyloid was absent in these vessels.

The entire right frontal lobe was infarcted and consisted of a cystic space limited externally by the arachnoidal layer and posteriorly by a zone of gliosis. The cystic cavity contained a delicate vascular and glial network infiltrated with lipid-filled macrophages. There were no amyloid deposits in the central nervous system or in its blood vessels.

The amyloid material in all situations stained distinctly with the Congo red, crystal violet, and Mayer's stains but did not react with the iodine stain.

COMMENT

Amyloidosis is a disease in which a foreign protein, amyloid, is produced and deposited in certain tissues. Amyloid disease has been classified as follows: (1) secondary amyloidosis; (2) primary amyloidosis; (3) amyloidosis associated with multiple myeloma; (4) tumor-forming amyloidosis.[30] The most common form of amyloidosis is the secondary type which is ordinarily preceded by tuberculosis or chronic suppurative disease, though less often may follow a nonsuppurative chronic inflammatory process. It has been shown that amyloid is composed of two protein fractions and one polysaccharide fraction.[42,43] The vascular distribution of amyloid suggests that it may be deposited as a combination product, the result of a reaction between a fixed component of the vascular wall and some component of the serum globulin.[30] Hyperglobulinemia may occur with this reaction and the amyloid may represent tissue deposits of excess

globulin protein.[44] Hyperglobulinemia and amyloidosis may occur together in multiple myeloma. Of the cases of primary amyloidosis recorded in the literature, only five had absolute serum globulin levels over 2.2 per cent.[17,21,34,35] It is probable that factors other than hyperglobulinemia are necessary for the development of amyloidosis.[45]

While the relationship of amyloid deposition to abnormal protein metabolism in the secondary type of amyloidosis seems related to a bacterial antigen-antibody reaction, this sequence is less clear in the so-called primary form of the disease. Jaffé[47] has stressed the relationship between the allergic state acquired during a chronic infection and the appearance of amyloid substance, since secondary amyloidosis is most frequently found in tuberculosis where the occurrence of allergic reactions is so striking. Review of the histories in the published cases of primary amyloidosis reveals a number with possible etiologic agents, including past infections now quiescent,[8,9,14,15,28] high protein diets,[30,34] pyorrhea alveolaris,[34] and mycotic infections.[31] In the case reported in this paper, food allergy was a possible etiologic agent. While hypersensitivity to foods or other ingested antigenic materials would suggest an etiologic basis for amyloid deposition due to an antigen-antibody relationship, Rowe[46] has seen no cases of amyloid disease in a large series of allergic patients. It has been noted[48] that a high protein diet may produce hyperglobulinemia.

Primary systemic amyloidosis is rare but is now a well-recognized entity. It differs from the more common secondary amyloidosis in several ways: (1) the absence of specific etiologic factors such as tuberculosis or chronic suppurative disease; (2) minimal or no deposition of amyloid in the liver, spleen, kidneys, and adrenal glands, the sites of maximum deposition in the secondary type of amyloid disease; (3) maximum deposition in the heart, lungs, skin, mucous membranes, striated muscles, and other tissues not usually involved in secondary amyloidosis; (4) formation of nodular amyloid tumors; (5) atypical reactions with specific amyloid stains.[8,30]

There may be difficulty in the clinical diagnosis of this type of amyloidosis unless its fairly uniform signs and symptoms, characteristics, and distribution in tissue are kept in view. Overlapping of the characteristics of the four types of amyloid disease has been observed.

It is of interest to note that spontaneous amyloidosis in mice resembles primary amyloidosis of human beings in its distribution, while the amyloidosis produced in these animals by injections of sodium caseinate bears a resemblance to the secondary form of the disease as seen in the human being.[52]

To date, forty-four cases of primary systemic amyloidosis have been recorded in the literature;[1-37] forty of these have been summarized by Koletsky and Stecher[30] and by Lindsay and Knorp.[36] Additional cases have since been reported by Brown and Selzer[35] and Golden.[37] Cases recorded by Pick[12] and by Bannick and co-workers[20] had been overlooked. Other papers dealing with systemic and atypical amyloidosis, with cardiac involvement, have been listed[49-51] in the *Cumulative Index Medicus* but due to war conditions are not available for study. With the present recorded case, a total of forty-five cases with forty-three

autopsy reports are available for review. Two patients were alive at the time the reports were made.

Of the forty-five cases, twenty-three showed clinical evidence of cardiac failure during the course of the illness. In eighteen of the forty-three fatal cases, it was stated that cardiac failure was the immediate cause of death. In one case with extensive valvular deposits of amyloid, death due to cardiac failure was the result of coronary atherosclerosis and myocardial infarction, though undoubtedly the valvular amyloid contributed to cardiac failure before death.[36] From the clinical and pathologic evidence available in the published cases, this author felt that in fourteen patients death from myocardial failure was the result of cardiac amyloid infiltration. In two additional instances, this possibility was likely, though not definite. Of the forty-three fatal cases in which autopsies were done, thirty-nine showed some degree of amyloid deposition in the heart. In a few cases, the amyloid deposition was limited to small cardiac blood vessels.[33,35]

Clinical evidence of cardiac failure due to amyloid deposition in the heart may be difficult to evaluate. Signs and symptoms suggesting cardiac disease may be produced by amyloid involvement (1) of the lungs, with chronic cor pulmonale, (2) of the trachea, or (3) of the mediastinum, or by the anemia which often is present.[30] Coronary atherosclerosis or hypertension may be complicating factors in the cardiac failure occurring in primary amyloid disease.[32,36]

Amyloidosis may produce cardiac failure in several ways: (1) deposition in the pulmonary vessels and alveolar walls with resulting chronic cor pulmonale; (2) deposition in the cardiac blood vessels, including arteries, veins, and capillaries; (3) diffuse or localized nodular interstitial amyloid infiltration with or without secondary degeneration of the myocardial fibers; (4) pericardial or endocardial deposits; (5) extensive valvular deposits producing stenosis or insufficiency; (6) often a combination of several sites of deposition.

Review of the symptoms in many of the recorded cases of primary systemic amyloidosis are those of cardiac insufficiency and insufficient blood flow to the myocardium. These include dyspnea, cyanosis, weakness, precordial pain, paroxysmal dyspnea, orthopnea, palpitation, and cough. Physical examination has revealed edema, hydrothorax, ascites, cardiac enlargement, cardiac murmurs, tachycardia, auricular fibrillation, venous engorgement and pulsation, gallop rhythm, tick-tack sounds, and pulsus alternans.

The widespread systemic distribution of amyloid substance, with resulting signs and symptoms, usually presents a bizarre, though somewhat uniform, clinical picture. The sites of involvement and the systemic signs and symptoms in the majority of cases have already been tabulated;[30,36] these may point to an amyloid background for the cardiac manifestations.

Lesions of the skin are fairly common. These have been described as opalescent and papular,[21] opalescent, firm, and nodular,[15] sclerodermic,[8,14,22] papular plus plaquelike scleroderma,[13] weeping eczematous,[36] and pink striae beneath the nails of the fingers and toes.[36] These deposits in the skin are, of course, accessible for diagnostic biopsies. In the majority of cases where there was an antemortem diagnosis, it was made by this method from sites including the

skin,[6,13,25] buccal mucosa,[21] skeletal muscles,[13,27] vagina,[25] and stomach.[37] In at least one instance[36] amyloid in the tissues removed was not recognized. It has been pointed out[30] that, because of the variability of the staining reactions in primary amyloidosis, tissue suspected of containing amyloid should be stained with several of the known amyloid stains (Congo red, crystal violet, and iodine and sulfuric acid).

Amyloid infiltration of the gastroenteric tract has been a frequent finding in this group of cases and has led to the following symptoms and signs: diarrhea, constipation, abdominal pain, nausea, vomiting, distention, intestinal hemorrhage, intestinal obstruction, epigastric tenderness, hematemesis, anorexia, and postprandial pyrosis. In three cases [8,36,37] gastric ulceration had occurred.

Enlargement of lymph nodes may be localized or generalized and may result in a localized amyloid tumor.[36]

Enlargement of the tongue has been a frequent finding, often has suggested neoplastic disease, and has been accompanied by dysphonia and dysphagia. The buccal and nasal mucosa, the larynx, and the trachea have been sites of infiltration. Nasal hemorrhage[36] and laryngeal obstruction[9] have been described. Facial rigidity has resulted from infiltration of the skin, subcutaneous tissues, and muscles.[15] Extensive involvement of skeletal muscle has produced the picture of myotonia with an unusual degree of progressive fatigue and weakness. Deposits in posterior roots, sympathetic ganglia, and peripheral nerves have resulted in muscular weakness.[28] Central nervous system involvement has not been described.

Arthritis may be simulated, and involvement of bones, joints, and tendons has led to limitztion of motion, disturbances in gait, and pathologic fractures.[30] Collapse[23] or narrowing[36] of vertebral bodies as the result of amyloid infiltration has occurred. Purpura is a common symptom and is presumably due to amyloidosis of the blood vessels,[30] though anemia and leucopenia resulting from amyloidosis of the marrow[36] suggests a thrombocytopenic basis for the bleeding tendency.

In many cases involvement of small blood vessels, especially arterial, has been widespread. Deposition in all portions of the genitourinary tract in both men and women has been reported.

In addition to biopsy of accessible amyloid lesions, the intravenous Congo red test may be helpful in establishing the diagnosis of amyloidosis. Bennhold's Congo red test[61] has recently been evaluated by Stemmerman and Auerbach[62] in a large group of patients with secondary amyloidosis. These authors considered a 90 to 100 per cent absorption of dye as a positive test. Where only minimal amounts of amyloid were present, false negative tests were likely to result. False positive results occurred with technical errors and in the presence of renal tubular damage. The Congo red test has been done in ten patients with primary amyloidosis. In five of these,[13,21,23,34,35] the results were considered positive with the percentage of intravenously administered Congo red absorbed from the blood at one hour ranging from 60 to 100 per cent. In the five in whom the test was considered negative,[17,25,27,30,37] the percentage of dye absorbed by the tissues

at one hour ranged from 0 to 35 per cent. In this small group of cases, there was no apparent correlation between the amount of amyloid found at autopsy (or estimated clinically) and the amount of Congo red removed from the blood. This test was not done in any of those patients in whom amyloidosis of the heart was the cause of death.

In amyloidosis secondary to tuberculosis or chronic suppuration, the heart is rarely involved, while the maximum deposition usually occurs in the spleen, liver, kidneys, and adrenal glands. In fifty-seven tuberculous patients observed post mortem, amyloid deposits in the heart were not encountered.[53] Amyloidosis is less common in chronic nonsuppurative disease,[54] although in severe rheumatoid arthritis amyloidosis has been reported in a few instances.[55] In experimental amyloidosis produced by injection of sodium caseinate, amyloidosis of the heart was observed. There were perivascular deposits in the myocardium and in the leaflets at the valves, particularly the mitral.[47]

Primary amyloidosis is generally characterized by an atypical amyloid distribution, often with cardiac involvement.[30] In the forty-three available autopsy reports, cardiac amyloidosis was encountered in thirty-nine instances. In one case[34] the amyloid distribution was similar to that seen in the secondary type of the disease. Conversely, several reports of secondary amyloidosis with the distribution characteristic of the primary type are available. In Kann's case [56] in which the amyloidosis presumably was secondary to syphilis, there was extensive substitution of the myocardium by amyloid substance. Both the auricular and ventricular walls were involved and there were nodular deposits in the endocardium. Small amounts of amyloid were present in the cardiac valves. Virchow[57] apparently was the first to observe amyloid deposition in the heart. Not until 1907 was the cardiac distribution adequately described. In eight patients with secondary amyloidosis, von Huebschmann[58] found amyloid in the connective tissues and blood vessels of the myocardium but rarely in the valves or endocardium. None of the eight patients had cardiac manifestations.

More recently, other cases of cardiac amyloid, secondary to chronic suppurative disease, have been reported. In Budd's case [59] in which a prostatic adenocarcinoma and urinary suppuration caused death, amyloid was encountered in the small coronary blood vessles, myocardium, and endocardium. Only minimal amounts of amyloid were present in the pulmonary and mitral valves.

In the case recorded by Spain and Barrett,[60] amyloidosis secondary to suppurative bronchiectasis was accompanied by amyloid deposits in the heart which had produced clinical evidence of cardiac failure, including dyspnea, cyanosis, edema of the legs, pleural effusion, and an increase in circulation time. The electrocardiogram showed left-axis deviation and low voltage in all leads.

The visceral pericardium has often been one site of cardiac amyloid deposition in primary systemic amyloidosis. Nodular amyloid strata on this layer have been described.[1] Both small and large discrete amyloid nodules often are present. In one case[8] both pericardial layers were firm and thickened. Gerstel[14] described a grayish-gold, jellylike membrane on the surface of the heart. The pericardial amyloid may take the form of small flecks[15] or pearly-gray 1 mm.

nodules.[30] In one case[19] there were deep parallel grayish-yellow furrows in the right auricular epicardium. At times the epicardium is thickened and grayish yellow in color.[22] In Kerwin's first case, both pericardial layers were studded with firm, translucent grayish 1 mm. nodules.[26] The nodules were larger but fewer in Golden's case.[37] In the pericardial layer, the amyloid has had both a vascular and an interstitial distribution. The latter has included amyloid rings about the pericardial fat cells in several of the recorded cases[1,4,18] and in the case reported in this paper. These pericellular amyloid deposits have also been seen in the periadrenal fat.[32] Peters[66] has pointed out that pericellular amyloid deposition may occur in many situations and has suggested that the deposition of amyloid on cell surfaces may be the initial process in amyloidosis. From the published reports, it seems unlikely that amyloid in the pericardial layers has contributed significantly to the production of cardiac failure.

The bulk of the cardiac amyloid has had a myocardial distribution in many of the cases and is most important in the mechanism of cardiac failure. Both the auricular and ventricular walls may be hypertrophied and thickened. When the myocardial amyloid is diffusely distributed, these walls have been described as hard or firm, pale, grayish tan or golden brown, waxy or translucent, homogeneous or glassy. The auricular walls are often stiff and leathery. The involved myocardium tends to be rigid and resistant to cutting, and the chambers retain their globular shape rather than collapsing. The diffuse myocardial amyloid deposits may appear as irregular, translucent, pearly-gray or yellowish-opaque streaks, gleaming flecks, or trabeculae or may be more localized as large or small nodular masses, often projecting above the cut surface. One to 3 cm. amyloid nodules have been noted in the ventricular walls.[10,15]

Microscopic examination of the myocardium in many cases has disclosed a rather consistent pattern of distribution of the amyloid substance. The myocardial blood vessels often contained mural amyloid deposits lying in any or all of their layers. In a few instances, these have appeared in the main coronary arteries. In one case, subendothelial amyloid at least contributed to narrowing of the lumens of the main coronary arteries.[36] More often, the medium-sized and small coronary arteries were involved with distinct narrowing of the vessel lumens. The veins, arterioles, and capillaries have also been the site of amyloid infiltration. The marked degree of vascular narrowing associated with this infiltration and the resulting diminution of blood flow to the myocardium has undoubtedly been a significant factor in failure of the myocardium in many of the cases.

Even more important in the mechanism of cardiac failure has been the diffuse interstitial amyloid infiltration of the myocardium. Aside from the deleterious effects on the muscle cells, the extensive amyloid network must have interfered greatly with the normal range of contraction and relaxation of the cardiac chambers. In twenty of the cases it has been noted that narrow bands of amyloid substance had been deposited about individual myocardial fibers appearing on cross section as imprisoning rings or sheaths. At times, one portion of this amyloid sheath may invaginate into the cytoplasm of the cell. The myocardial

fibers may be compressed, narrowed, or displaced and frequently have been severely damaged. They were often atrophic, vacuolated, fragmented, necrotic, or contained lipid or pigment deposits. Nuclear degeneration was common. With excessive deposition, the muscle cells disappeared, leaving empty amyloid rings or almost solid amyloid sheets. The fibers in those areas with less or no amyloid often compensated by hypertrophy.

Beneke and Bönning[4] were of the opinion that the amyloid material was primarily deposited on and about the muscle cells. In the light of the observations of Peters,[66] this may be true. Larsen,[11] however, pointed out that the intercellular and pericapillary deposits were continuous and felt that the pericellular amyloid originated in the blood vessels. This same continuity has been noted by others[32,37] and was seen in the case reported in this paper. The intercellular amyloid appeared to extend from extensive arterial and arteriolar deposits in one instance.[37]

Koller[16] described the pericellular amyloid as being deposited in the perimysium of the myocardial fibers. By combining the Congo red and a silver reticulum stain on the same section, it was possible in the case reported in this paper to demonstrate that the amyloid had largely replaced the pericellular reticulum and, furthermore, that when the reticulum persisted, it lay between the cell membrane and the pericellular amyloid ring.

Where the amyloid deposits were fewer and more localized, the material lay in rounded, confluent, nodular masses, showing neither a distinct cellular nor vascular origin.

In the majority of recorded cases, amyloid was present in the endocardial layer, often as stratified or nodular deposits and occasionally continuous with the myocardial amyloid. In one case[36] where both valvular and mural endocardial amyloid was particularly abundant, this material lay immediately beneath the endothelium. In many instances, the amyloid infiltrates mainly the deep endocardial layers.

Of the forty-five cases of primary systemic amyloidosis, sixteen had amyloid deposits in the cardiac valves. Valvular involvement is often slight and only microscopically demonstrable. In a smaller number of cases, the valvular deposition was more striking. Discrete amyloid nodules, with thickening and rigidity of several of the valves, have been described.[1] Grayish-white 1-3 mm. discrete nodules may be limited to the mitral valve.[7] In Koller's case[16] both the mitral and tricuspid valves were hard, thickened, and stenotic. The valvular amyloid in one instance appeared as grayish-red warty nodules on all valves except the aortic.[19] Fine shotty amyloid nodules were present along the free margins and auricular surfaces of the mitral and tricuspid valves in the first case recorded by Kerwin.[26] In another case[29] there was a plaquelike thickening of the line of closure of the mitral valve. Amyloid nodules may lie both in the cusp and the annulus fibrosis of the cardiac valves.[37] In two of the recorded cases[30,36] there were unusually abundant amyloid masses in the cardiac valves. In Koletsky and Stecher's case[30] all four valves showed nodular deposits of amyloid, particularly in the aortic and mitral valves. These nodules had so involved the base and free

margins of the leaflets as to produce thickening, rigidity, immobility, and stenosis. These authors explained the extensive involvement of the leaflets as a direct extension of amyloid from the ring of the valve. All four valves were also extensively infiltrated with amyloid in the case recorded by Lindsay and Knorp.[36] In this instance, the valvular surfaces, particularly of the pulmonary and tricuspid valves, were covered by smooth, nodular, glistening, translucent, yellowish-white, soft amyloid substance, which had led to a distinct decreased mobility of the cusps. The chordae tendineae were similarly covered, but their fibrous structure was visible through the amyloid coating. In this case, the origin of the amyloid from the adjacent endothelium was apparent. In both of these cases[30,36] it was considered probable that the valvular amyloid infiltration played a significant role in the mechanism of cardiac failure.

In addition to direct cardiac infiltration by amyloid material, cardiac failure may also result from pulmonary amyloid disease. Chronic cor pulmonale with right ventricular hypertrophy and dilatation on a pulmonary amyloid basis has been recorded on several occasions[11,32,33] and also was noted in the case reported in this paper. The pulmonary amyloid infiltration in the case reported by Sappington and co-workers[33] was extreme. There was universal involvement of both the arteries and veins plus almost complete amyloid infiltration of the alveolar walls. Presumably the latter was related to capillary infiltration. There was a marked reduction in the diameter of the lumens of the involved vessels, which by interference with pulmonary blood flow had produced right ventricular hypertrophy. A roentgenogram of the chest showed enlargement of the cardiovascular silhouette and an indefinite haziness of the lung fields. In one case[11] some of the amyloid masses in the alveolar walls were so abundant as to cause bulging of the alveolar epithelium into the acinar space. In the patient described in this paper, there was also abundant pulmonary vascular and interstitial amyloid which produced right ventricular hypertrophy and undoubtedly contributed in part to the cardiac failure. Pearson and co-workers[32] were of the opinion that the obliterating pulmonary vascular amyloid infiltration in one of their cases was a factor in the production of right ventricular failure.

Hypertension has been present in four of the recorded cases.[23,28,32,37] In the first, hypertension was due to renal amyloidosis. In the second, gross renal scarring and microscopic amyloid were present, but whether the two were related to each other and to the elevated blood pressure was not stated. In the last two cases, renal amyloid was not present, and presumably the hypertension was coincidental and essential in type. In one case[32] the authors felt that cardiac failure was the result, in part, of hypertension.

Electrocardiographic studies were done on twelve of the forty-five recorded cases.[11,26-29,31-34,36] In nine of the twelve cases, myocardial amyloid infiltration was considered to have been the cause of death. In six of these, low voltage in the electrocardiographic record was a prominent feature. Katz[63] has pointed out that one cause of low voltage in the QRS complex is a diffuse myocardial alteration which prevents a normal flow of current through the ventricular tissues. The myocardial amyloid in this group of patients appears to have produced a

distinct conduction disturbance in the ventricular walls. In one case[34] the P-R interval was slightly prolonged. Alteration of the P wave was not noted in any of the cases. Auricular fibrillation was present in one case,[11] and ventricular premature contractions were noted in two cases. Axis deviation was more often to the left than to the right. In one case with an abnormal electrocardiogram, the responsible myocardial lesion was due to arteriosclerosis and not amyloid.[36]

Treatment of primary systemic amyloidosis to date has been symptomatic, expectant, and directed toward the complications. In only twelve cases has an ante-mortem diagnosis been made, usually by biopsy. The rate of progress of the disease is variable. Duration of life from the onset of symptoms has varied from four months[16] to fourteen years[30] and sixteen years.[37]

It is well known that recovery from secondary amyloidosis may occur, usually following retrogression of the responsible inflammatory process. Trasoff and co-workers[55] have cited some twenty-nine instances of recovery recorded since 1880. Experimental amyloidosis in mice produced by protein administration has receded when such treatment was terminated.[64,65] Reabsorption of experimentally produced splenic amyloid appeared to be the result of leucocytic and capillary invasion, amyloid fragmentation, and foreign body giant cell activity.[45] Grayzel and co-workers[65] found that administration of liver substance either resulted in absorption or delay in deposition of experimentally induced amyloid in mice. These studies have led to successful therapy of secondary human amyloidosis.[41] Despite the continuation of the underlying process, thirteen children with chronic suppurative disease were treated orally with powdered whole liver extract. With the exception of four dying with advanced tuberculosis, this group showed marked improvement or complete recovery from amyloid disease. Early signs of recovery were diminution in size of the liver and spleen, with the other signs and symptoms regressing more slowly. It was emphasized that the recovery rate was not regularly progressive, suggesting a variable chemical composition of the amyloid substance.

More recently Jacobi and Grayzel[67] recorded the effects of the oral administration of 4 to 8 Gm. of desiccated powdered whole liver preparation to patients with amyloidosis secondary to tuberculosis. Treatment was continued for a year or more, and of sixteen patients, nine were cured as demonstrated by the disappearance of symptoms and the absence of Congo red retention.

While there are undoubtedly certain differences in the composition of amyloid in the primary and secondary forms of the disease, therapy with liver substance may be found to be of benefit in the primary type.

Clinical and laboratory recognition of primary amyloidosis, further elucidation of the responsible mechanisms at work, with their subsequent removal or amelioration, may result in recovery as in experimental and secondary amyloidosis. Accumulating evidence suggests that the fundamental disturbance is identical in all types of amyloid disease and that when the basic mechanism is known, primary amyloidosis will be classified as a "secondary" type.

SUMMARY

1. A case of primary systemic amyloidosis is reported. The duration of the illness was one year. Death was due to cardiac failure, the result of extensive amyloid infiltration of the myocardium.

2. There are now forty-five cases of primary systemic amyloidosis recorded in the literature. These have been reviewed, and their cardiac manifestations and involvement by amyloid substance have been summarized and discussed.

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SOME OBSERVATIONS ON THE PATHOGENESIS OF EDEMA IN CARDIAC FAILURE

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THE pathogenesis of cardiac edema has been the subject of extensive investigation and many explanations have been given. The classical work of Starling[12] cleared up much of the confusion which had existed in the theories of the pathogenesis of all forms of edema. At present the most widely accepted explanation is that cardiac edema is due to an increase in the filtration of water and electrolytes through the capillaries into the extracellular space secondary to a rise in the hydrostatic pressure within the capillaries and elevated venous pressure. The rise in venous pressure is caused by failure of the right heart. The absence of edema in left heart failure and in peripheral circulatory failure is good evidence that circulatory retardation is not an important factor.[2]

Krogh, Landis, and Turner[9] have shown that in experimental venous congestion the rate of edema formation is increased as the colloidal osmotic pressure is decreased. Many patients with congestive heart failure have slightly decreased plasma proteins, though the levels reached are very rarely low enough to explain in itself the formation of edema.[10,11,14] Warren and Stead[15] and Bramkamp[1] have shown that cardiac edema fluid does not contain an increased amount of protein. This is good evidence that increased capillary permeability is not a significant factor.

In patients with congestive heart failure the urinary output is low and no satisfactory explanation of this has yet been given. Several observers[3,6] have demonstrated that there is an increased blood volume and hemodilution in congestive heart failure rather than the lowered blood volume and hemoconcentration which would be expected if the oliguria were a manifestation of the increased transudation of water into the extracellular space. Fremont-Smith[4] showed that following the ingestion of water, normal subjects had less hemodilution and more diuresis than patients with cardiac edema. Thus one has to assume that there is also a renal factor in cardiac edema. Futcher and Schroeder[5] further confirmed this idea by demonstrating impairment in the ability of the kidneys to excrete injected sodium chloride in four patients convalescing from severe congestive heart failure.

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In 1944 a paper was published which aroused much comment and interest and in no small part gave rise to the study which is reported here. Warren and Stead[15] gave excess sodium chloride to two patients just after they had become compensated following a bout of severe congestive heart failure. They reported that both of the subjects showed a significant weight gain before the venous pressure rose. As a result of this experiment they offered the following explanation of the mechanism of cardiac edema: "Edema develops in chronic congestive failure because the kidneys do not excrete salt and water in a normal manner. This disturbance in renal function is related to the decreased cardiac output and not to engorgement of the kidneys from an increased venous pressure because the salt and water retention may occur before there is a rise in venous pressure." In our study, we have attempted to see also whether the venous pressure or the weight rose first as a patient went into cardiac decompensation; but instead of adding excess salt to induce failure, digitalis was withdrawn.

The Effect of Withdrawing Digitalis on Venous Pressure and Edema Formation.—Observations were made on three patients with clinically inactive rheumatic heart disease and chronic auricular fibrillation. Two of the patients (N. C. and L. B.) had both aortic and mitral valvular lesions, while the third (B. H.) had mitral stenosis and insufficiency. All three of the subjects had had repeated episodes of cardiac decompensation, with both left and right heart failure. In two of them peripheral edema had been present, while in the third (N. C.) no clinically detectable edema but marked enlargement of the liver and elevated venous pressure was observed during the periods of right heart failure.

When admitted to the hospital the patients were suffering from chronic heart failure of a moderate degree. Cardiac compensation was achieved by the use of digitalis and a diet which contained approximately 3 to 4 Gm. of sodium chloride a day. Absolute bed rest was not enforced, the patients being allowed a moderate amount of activity.

The venous pressure was measured in the basal state by the direct method, the level of the right auricule being estimated to be at a level 10 cm. above the back.[8] The apical rate and the pulse rate were counted, and then the patient's weight was measured.

When clinical evidence and laboratory tests showed that cardiac compensation had been restored, cardiac failure was induced by omitting digitalis medication. Determinations of the venous pressure and of the weight were continued as during the control period.

The data obtained are listed in Table I and Fig. 1. Our results show that after the discontinuance of digitalis a considerable rise of venous pressure (approximately 60, 55, 85 mm. of water) occurred with no or very slight gain in weight. In Patient N. C. there was even a loss of weight which undoubtedly was due to the fact that he started to vomit a few hours before the termination of the experiment. The largest weight gain, 0.8 kilogram, occurred in Patient L. B. In this patient the venous pressure, after a considerable rise, fell spontaneously. Consequently a general diet was substituted for the salt-poor diet, which represented an increase of approximately 5 Gm. of sodium chloride a day. Following this change the venous pressure rose from 122 to 215 mm. of water during the next five days, while the patient's weight increased by only 0.9 kilogram. During the next four days the patient gained another 1.9 kilograms, while the venous pressure remained essentially unchanged. Only after this period did very slight pretibial edema appear.

TABLE I. THE EFFECTS OF STOPPING DIGITALIS IN THREE PATIENTS WITH HEART FAILURE

PATIENT	DATE	WEIGHT (KG.)	VENOUS PRESSURE (MM. OF WATER)	APICAL RATE	RADIAL RATE	REMARKS
B. H.	3/16	54.5	76	62	62	
	3/17	53.9	82			
	3/18	54.4	86	68	68	Taken off digitalis
	3/19	53.7				
	3/20	54.0	105			
	3/21	54.5	106	72		
	3/22	54.0	105	70		
	3/23	54.6	144	74		
	3/24	54.7	137	80		At 10 P.M. onset of fast auricular fibrillation and left heart failure; digitalized
N. C.	4/19	52.8	120	64	64	
	4/20	53.3	117	57	57	
	4/22					Taken off digitalis
	4/24	53.5	140	64	64	
	4/25	53.1	145			
	4/26	53.5	120	71	71	
	4/27	53.3	140	72	72	
	4/28	53.2	131	67	67	
	4/29	53.3	150	88	84	
	4/30	52.2	173	140		Vomiting; liver enlarged; digitalized
	5/1	51.7	83	80	80	
L. B.	6/22	40.3	89	60	60	
	6/23	40.3	82	45	45	Taken off digitalis
	6/25	40.4	95	62	62	
	6/26	40.0	108	64	64	
	6/27	40.0	108	62	62	
	6/29	40.3	124	58	58	
	6/30	40.4	124	58	58	
	7/1	40.7	132	58	58	
	7/2	41.1	170	60	60	
	7/4		165	62	62	
	7/6	40.9	150	58	58	
	7/8	41.2	155	60	60	
	7/10	41.2	153	60	60	
	7/13	40.8	140	58	58	
	7/20	40.5	122	60	60	7/22 put on general diet
	7/23	40.9	152	60	60	
	7/25	41.2	171	62	62	
	7/27	41.4	215	68	68	
	7/30	42.8	220	82	78	
	8/1	43.3	210	92	78	Moist râles over lung bases; slight pretibial edema; digitalized

It seems quite clear that when digitalis is withdrawn the first change noted is a rise in venous pressure before there is any significant weight gain. The three subjects all were patients with mitral stenosis and auricular fibrillation, and the objection may be raised that the sequence of events observed holds true only for patients with similar abnormalities. If this were true, we would have to formulate a different explanation of cardiac failure in each separate type of heart disease.

The data presented by Warren and Stead[15] are open to some criticism. Their first patient was started on salt at a time when his hematocrit reading was 54 to 55. It seems quite possible that this patient was dehydrated. When his salt intake was increased and diuretics omitted, the hematocrit reading fell. After an hematocrit reading of 46 was reached, the weight and venous pressure rose simultaneously. The weight gained at the onset of the experiment may well have been the result of replacement of water and salt in a dehydrated person. In their second patient, the amount of weight gained before rise in venous pressure was 2.6 kilograms, since the first venous pressure reading recorded after this weight level was reached showed a rise from 40 to 150 mm. of water.

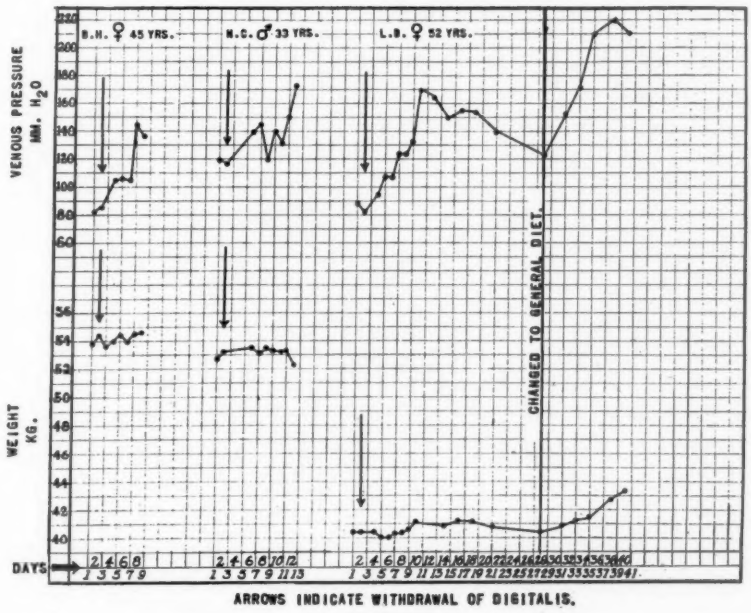

Fig. 1.—Changes in venous pressure and weight during development of cardiac failure.

Futcher and Schroeder[5] in their experiments on the excretion of injected hypertonic sodium chloride in patients who had been in congestive heart failure studied also the changes in venous pressure. Of their five cases studied, adequate venous pressure readings were made on three patients. Of these, only two are suitable for discussion here because the venous pressure was at an abnormal level in the third patient at the onset of the experiment. In the first patient twenty-four hours after the administration of 33 Gm. of sodium chloride the venous pressure had risen 50 mm. of water (125 to 175) without weight gain. The second patient showed a rise in venous pressure of 43 mm. of water (115 to 158) and a weight gain of 1.5 kilograms twenty-four hours after the injection of 24 Gm. of sodium chloride. Thus we see that both of these patients studied by Futcher and Schroeder[5] had a rise in venous pressure to abnormal levels with little or no weight gain.

L. B., our third subject, also showed a marked rise in venous pressure before gain in weight after salt had been added to her diet.

These observations are quite compatible with the backward failure hypothesis[7] according to which cardiac edema is due mainly to the increased venous pressure secondary to right heart failure.

CONCLUSIONS

1. As cardiac decompensation develops after the withdrawal of digitalis, the rise in venous pressure precedes the gain in weight and the formation of edema.

2. The main factor in the production of cardiac edema is the increase in venous pressure.

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CORONARY SINUS RHYTHM

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IT IS now generally accepted that stimuli originating in the auriculoventricular node may produce three patterns of cardiac rhythm. In the first type the pacemaker is situated in the upper part of the auriculoventricular node, and a normal or slightly shortened P-R interval occurs. In the second type the focus of origin is in the center of the node and both auricle and ventricle contract simultaneously. In the third type the stimulus originates in the lower part of the auriculoventricular node and the auricle is activated after the ventricle. Electrocardiograms imitating these three forms of auriculoventricular rhythm may also be found with the same focus of origin in the presence of conduction disturbances from the auriculoventricular node to the auricle or ventricle.[13,26]

In the era before electrocardiography, the existence of auriculoventricular rhythm with a normal P-R interval caused much confusion. The appearance of normal auriculoventricular succession following extirpation of the sinus node even led some authors to assume that the sinus node was not the only pacemaker in the auricle under normal conditions. Later it was shown that, with an electrocardiogram exhibiting deeply inverted P waves in Leads II and III and a normal or only slightly shortened P-R interval, the focus of origin of the stimulus was situated in the upper part of the auriculoventricular node which extends to the sinus of the coronary vein. This rhythm was called coronary sinus rhythm.[30] This type of disturbance is still not too well known and has not yet been studied on an extensive basis.

In this paper we are reporting our observations on thirty-one patients with coronary sinus rhythm studied over a period of six years. The data obtained in our thirty-one cases are reproduced in Table I.

OBSERVATIONS

Incidence.—Between the years 1940 and 1945, inclusive, 23,610 electrocardiograms were taken at the Metropolitan Hospital where they were routine on the medical service. This figure includes many instances in which tracings were obtained repeatedly from the same patient. During this period, the electrocardiographic pattern of coronary sinus rhythm was observed in thirty-one patients, of which seventeen were men and fourteen were women. These

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TABLE I. CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY-ONE PATIENTS WITH CORONARY SINUS RHYTHM

CASE	NAME	SEX	AGE	FORM OF P WAVES IN LEAD					CLINICAL DIAGNOSIS	RATE	P-R INTERVAL DURING		OTHER ECG. CHANGES	REMARKS
				I	II	III	CR_2	CR_4			CSR	RSR		
1	G. E.	M	67	Low	Deeply neg.	Deeply neg.	Neg.	Neg.	Coronary sclerosis	77	0.17	0.20	Bundle branch block	Amyl nitrite and exercise cause only increased rate
2	J. F.	M	45	Low	Neg.	Neg.	—	——	Bronchopneumonia	84	0.12	—	Normal	
3	A. M.	F	59	Low	Neg.	Neg.	—	Diphasic	Posterior wall infarction	72	0.12	0.18	Q_3-T_3 pattern	Carotid pressure causes sinus rhythm
4	J. G.	F	70	Low	Neg.	Neg.	—	——	Hypertension; hemiplegia	66	0.12	0.12	QRS slurred; T waves abnormal; depressed S-$T_{1,2}$	Carotid pressure causes slowing; amyl nitrite causes acceleration and rare sinus escape
5	A. L.	M	19	Low	Neg.	Neg.	—	——	Bronchiectasis	62	0.13	—	Normal	
6	A. G.	F	40	Absent	Deeply neg.	Deeply neg.	—	——	Hypertension	100	0.10	—	Normal	
7	M. M.	F	29	Low	Deeply neg.	Deeply neg.	—	Neg.	Aortitis	88	0.13	—	Abnormal T waves in each lead	
8	R. D.	M	16	Low	Deeply neg.	Deeply neg.	—	——	Observation	71	0.12	0.14	Normal	
9	J. R.	M	22	Low	Neg.	Neg.	—	——	Keratitis	63	0.11	0.14	Normal	
10	G. W.	F	52	Low	Deeply neg.	Deeply neg.	—	Deeply neg.	Hypertension	110	0.08	—	Left ventricular strain pattern	

11	W. L.	M	63	Low	Deeply neg.	Deeply neg.	—	Deeply neg.	Hypertension	68	0.08	—	Inverted T_1; no T_2	
12	F. L.	F	31	Wide; positive	Deeply neg.	Deeply neg.	—	——	Rheumatic mitral lesion	120	0.16	—	Right axis deviation; no T waves	
13	G. M.	F	40	Invisible	Deeply neg.	Deeply neg.	—	Positive	Coronary sclerosis	98	0.13	—	QRS slurred; no abnormal T waves	
14	C. S.	M	68	Invisinle	Deeply neg.	Deeply neg.	—	Positive	Coronary sclerosis; diabetes	66	0.15	0.15	Very low T_1; multiform ventricular extrasystoles	
15	M. T.	M	56	Low	Neg.	Neg.	—	——	Hypertension	56	0.12	0.16	Left ventricular strain pattern	Coronary sinus rhythm appears during carotid pressure
16	J. G.	M	68	Low	Deeply neg.	Deeply neg.	—	——	Coronary sclerosis; hypertension	96	0.14	0.20	QRS slurred; abnormal T waves	Changes to sinus rhythm from coronary sinus rhythm spontaneously; amyl nitrite and carotid pressure cause sinus rhythm
17	M. D.	F	76	Low	Deeply neg.	Deeply neg.	—	——	Pneumonia	106	0.12	0.20	Abnormal T waves in each lead	Carotid pressure causes sinus rhythm; amyl nitrite accelerates coronary sinus rhythm
18	Z. C.	F	80	Invisible	Deeply neg.	Deeply neg.	—	——	Coronary sclerosis	84	0.11	—	T_1 abnormally low	Carotid pressure causes slowing; no other change
19	S. S.	M	24	Invisible	Deeply neg.	Deeply neg.	—	——	Observation	58	0.16	—	Right axis deviation	Exercise and amyl nitrite cause sinus rhythm
20	E. T.	F	45	Low	Deeply neg.	Deeply neg.	—	——	Hypertension	74	0.11	0.15	Left ventricular strain pattern	
21	G. D.	M	49	Low	Neg.	Neg.	—	——	Rheumatic mitral lesion	72	0.14	0.18	Intraventricular block	

TABLE I. CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY-ONE PATIENTS WITH CORONARY SINUS RHYTHM—CONT'D

CASE	NAME	SEX	AGE	FORM OF P WAVES IN LEAD					CLINICAL DIAGNOSIS	RATE	P-R INTERVAL DURING		OTHER ECG. CHANGES	REMARKS
				I	II	III	CR^2	CR^4			CSR	RSR		
22	S. F.	M	62	Low	Neg.	Neg.	—	——	Coronary sclerosis	66	0.11	—	Left ventricular strain pattern	
23	L. D.	M	36	Low	Neg.	Neg.	—	——	Rheumatic mitral lesion	100	0.12	—	Normal	Carotid pressure, amyl nitrite, and exercise alter rate only
24	R. G.	F	41	Low	Neg.	Neg.	—	Isoelectric	Hypertension	90	0.09	—	Left ventricular strain pattern	
25	A. P.	F	52	Low	Neg.	Neg.	—	——	Hypertension; coronary sclerosis	100	0.12	0.12	Left ventricular strain pattern	Sinus escape
26	J. R.	M	72	Low	Neg.	Neg.	—	——	Senile emphysema	66	0.12	0.14	Normal	
27	D. O'K.	M	45	Low	Neg.	Neg.	—	——	Hypertension	60	0.15	—	Normal	
28	B. P.	F	63	Low	Neg.	Neg.	—	——	Hypertension	72	0.14	—	Intraventricular block	
29	M. O'C.	F	74	Low	Deeply neg.	Deeply neg.	—	——	Hypertension	100	0.13	—	Marked depression of $S\text{-}T_{1,2}$	
30	J. L.	M	68	Low	Deeply neg.	Deeply neg.	—	——	Hypertension	82	0.15	—	Left ventricular strain pattern	
31	B. C.	M	70	Low	Neg.	Neg.	—	——	Coronary sclerosis	110	0.14	—	Abnormal T waves in each lead; low QRS complexes	

figures do not permit calculation of the true incidence of coronary sinus rhythm, but they do permit the conclusion that the condition is not as rare as was formerly believed. In another series of 10,000 cases, an auriculoventricular nodal rhythm was found in forty-five patients. Fifteen of these showed coronary sinus rhythm.[20] The incidence of coronary sinus rhythm is, therefore, approximately the same in these two series.

Electrocardiographic Pattern.—For many years, the form of the P waves in tracings of auriculoventricular rhythm was merely mentioned as being negative, and even in the classic monographs by Lewis[15] and by Wenckebach and Winterberg[28] the form of the P waves in all three standard leads was not discussed.

It is now established that in auriculoventricular nodal rhythm the P wave in Lead I is low, positive, and sometimes invisible, while in Leads II and III it is negative.[29] In this paper are included only those tracings which show such P waves. Electrocardiograms with a positive P wave in Lead I, an inverted P wave in Lead III, and an isoelectric P wave in Lead II are not included since in these cases we are usually dealing with a regular sinus rhythm.

Another characteristic of the P waves frequently found in Leads II and III is their very sharply peaked form. Even when they have a duration of 0.05 second, the P waves seem shorter because they are so pointed. In the majority of our cases, we could not find the form showing a steep downstroke and a slow upstroke described as characteristic by Lewis.[15] In the chest leads (CR_2 and CR_4) the form of the P waves usually resembles that found in Leads II and III, but diphasic as well as positive P waves were also observed.

In cases of coronary sinus rhythm the electrical axis of the auricle points to the left and the depolarization of the auricle proceeds in a direction opposite to that occurring under normal conditions.[19-21]

The electrocardiogram reproduced in Fig. 1, obtained from a patient with syphilitic aortitis and involvement of the coronary artery orifices, shows P waves that are positive in Lead I and sharply inverted in Leads II, III, and CR_4. The P-R interval measures 0.11 second. There is moderate right-axis deviation. The abnormal depression of the S-T segment is partly due to digitalis treatment.

With slight variations, the P wave pattern described previously was seen in all cases. In seventeen tracings, the sharp pointing was present. The P waves in a case of mitral stenosis were markedly widened, but even here the negative pointing in Leads II and III was present despite the intra-auricular conduction disturbance.

The P-R interval during coronary sinus rhythm varied between 0.08 and 0.17 second. Tracings with a P-R interval of less than 0.08 second were not included in this investigation. In one case the P-R interval during coronary sinus rhythm was 0.17 second, and during regular sinus rhythm it was 0.20 second (Case 1, Table I). In fourteen electrocardiograms the P-R interval during coronary sinus rhythm measured between 0.10 and 0.12 second. In thirteen cases it was possible to compare in the same individual the P-R interval during regular sinus rhythm with that found during coronary sinus rhythm. The difference between both values ranged from 0.0 to 0.08 second. In three patients the

P-R interval was found to be the same during both rhythms. It is important in evaluating these figures to re-emphasize that the length of the P-R or R-P interval during auriculoventricular rhythm depends not only upon the position of the stimulus formation center in the auriculoventricular node, but also upon the speed of conduction from this center up to the auricle and down to the ventricle.

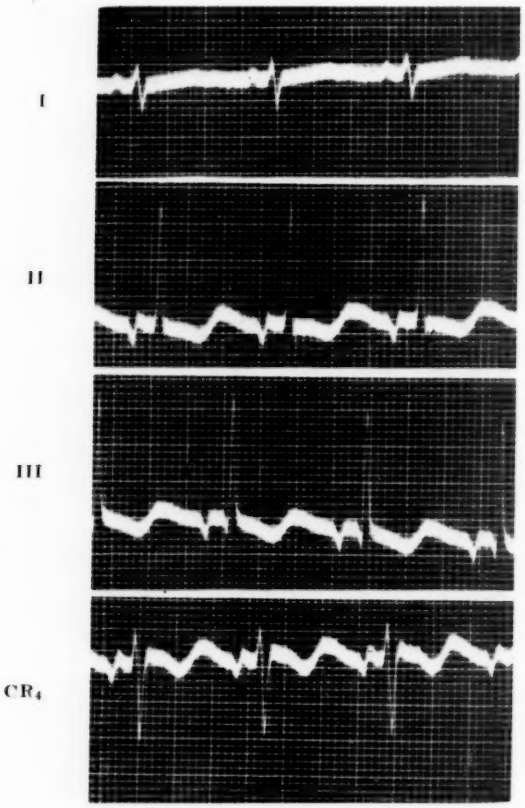

Fig. 1.—Coronary sinus rhythm with right-axis deviation and abnormal S-T segments and T waves.

The heart rate during coronary sinus rhythm varied between 56 and 120 beats per minute. No relation could be detected between the heart rate and the length of the P-R interval.

Evidence of myocardial damage was found in the electrocardiograms of twenty-three patients. In two of these patients right-axis deviation was present. The electrocardiogram was normal in eight patients.

Condition of the Heart.—Clinical evidence of organic heart involvement was present in twenty-four patients. In thirteen of these, hypertension was observed. Marked abnormalities in the electrocardiogram, cardiac enlarge-

ment, or other signs in the other eleven patients indicated the presence of an abnormal heart usually due to coronary sclerosis. In some elderly patients or in patients with pneumonia, the presence of organic changes in the heart was possible despite normal clinical findings. The heart was presumably normal on clinical and electrocardiographic examinations in only three subjects (Cases 5, 8, and 9, Table I).

In connection with our data, it is worthy of emphasis that Ruskin and his associates found ten patients with definite evidence of heart disease among fifteen cases of coronary sinus rhythm.[20] Hypertension was present in eight of the ten cases. In another series of twelve patients with different types of auriculoventricular nodal rhythm, seven showed hypertension.[9]

Response to Exercise, Amyl Nitrite Inhalation, and Carotid Sinus Pressure.—One feature of the coronary sinus rhythm is its lability. Capable of changing spontaneously, coronary sinus rhythm may frequently also be converted easily into regular sinus rhythm by exercise, amyl nitrite inhalation, or carotid sinus pressure. This change, of course, is possible only in those cases where the sinus node still functions. In some cases exercise or inhalation of amyl nitrite simply causes acceleration of the existing coronary sinus rhythm (Table I); in others, these measures cause the sinus rhythm to become so accelerated that it gains the upper hand and displaces the coronary sinus rhythm. The results cannot be predicted because they depend on the degree of acceleration of either node.

Similarly, pressure on the right or left carotid sinus may only slow the existing coronary sinus rhythm or change either rhythm into the other. In Fig. 2 is shown the effect of right carotid pressure in Lead III of the electrocardiogram on a patient who displayed coronary sinus rhythm spontaneously on many occasions. The rate was slowed; one beat with an abnormal P wave presumably was caused by one part of the auricle being activated by the sinus node and another part by the auriculoventricular node; then pure coronary sinus rhythm followed. Once established, this abnormal rhythm often persisted for a long time with a rate frequently the same as that of the regular sinus rhythm preceding the carotid pressure.

In Fig. 3 is shown a spontaneous change in Lead II from coronary sinus rhythm to regular sinus rhythm and back to coronary sinus rhythm. In many instances the changes, resembling the sudden ending of a paroxysmal tachycardia, are as abrupt as in the beginning of Fig. 3.

Sinus Escape.—During auriculoventricular rhythm in dogs caused by cooling of the sinus node, an "escape" of the sinus node in the form of normal beats with normal P waves and normal P-R intervals was observed occasionally.[14,16] Some of these tracings were explained in a different way,[26] but a sinus escape undoubtedly occurs. We were able to observe it in the electrocardiograms of three patients.

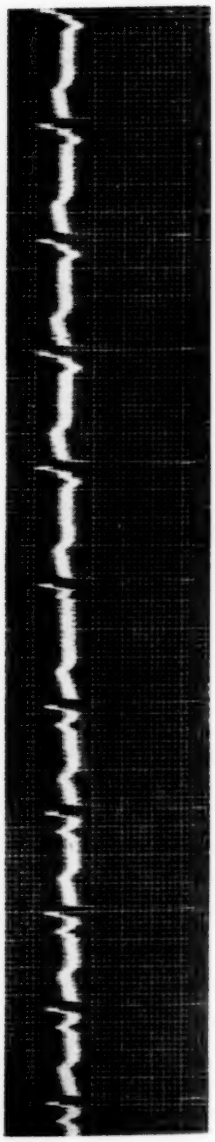

Fig. 2.—Lead III. Right carotid pressure changes sinus rhythm into coronary sinus rhythm.

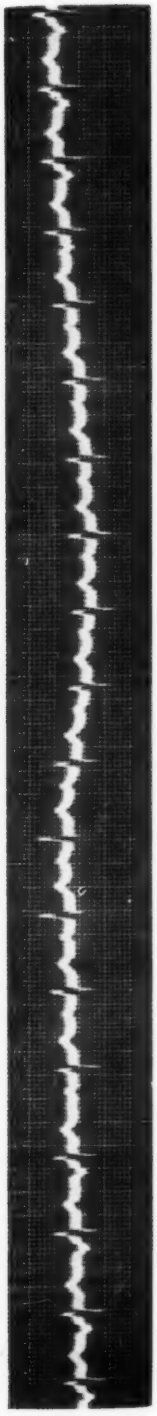

Fig. 3.—Lead II. Spontaneous change from coronary sinus rhythm to sinus rhythm and back to coronary sinus rhythm.

Fig. 4 was obtained from Case 1, Table I. A left bundle branch block is present and the P waves show the typical sharp inversion in Leads II and III. In Lead II, as well as in CR_2, slightly premature beats with normal P waves and somewhat longer P-R intervals occasionally appear. Their interpretation as sinus escape beats seems justified.

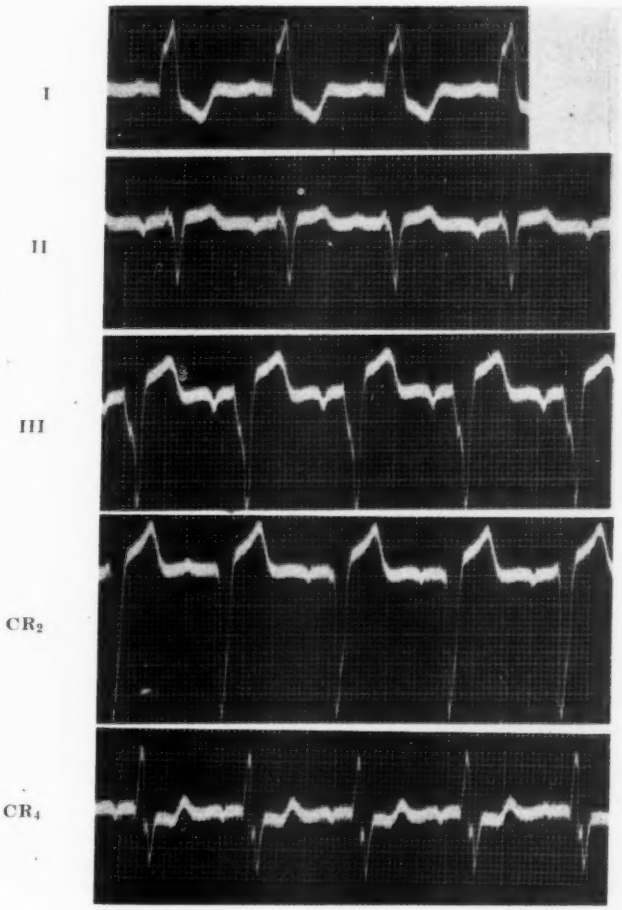

Fig. 4.—Coronary sinus rhythm with sinus escape in Leads II and CR_2.

DISCUSSION

The diagnosis of coronary sinus rhythm in tracings like those of Figs. 1 to 4 is supported by the result of anatomic and experimental investigations. Anatomic observations reveal data compatible with the assumption that the coronary sinus area is occasionally the site of stimulus formation. In his classic treatise, Tawara described specific fibers which enter the posterior part of the auriculoventricular node from the sinus of the coronary vein.[27] The characteristic struc-

ture of the specific fibers near the coronary sinus in the calf was described by Aschoff who was reminded of a third stimulus center in addition to the sinus and auriculoventricular nodal centers.[2]

The specific muscle fibers of the auricle which originally formed one unit are later separated into two parts, one which represents the sinus node, and a second which unites with the auriculoventricular node to form its auricular portion.[1] The peculiar structure of the coronary sinus fibers was also stressed by others.[11,12] Kung described a small bundle of muscle fibers entering the auriculoventricular node from the area of the coronary sinus. This bundle contained many ganglion cells which in several places were in direct contact with the muscle fibers. A network of nerve fibers also surrounded the muscle fibers. From these findings, the author concluded that these structures apparently possessed a remarkable functional ability.[12]

Experimental work showed that warming of the coronary sinus area in dogs caused a tachycardia with a normal P-R interval.[30] In dogs exhibiting electrocardiograms with inverted P waves preceding the QRS complex by a normal distance, the area of primary negativity (the focus of stimulus formation) has been found to be in the coronary sinus area by direct leads.[17] In the experiments by Zahn, however, only smoked paper tracings were used, and doubts were expressed concerning the results of his experiments and the studies of Meek and Eyster.[14] Therefore, the experiments of Zahn were repeated with the aid of the electrocardiogram.[24] It could be shown that a regular tachycardia with deeply inverted P waves and normal P-R intervals occurred during the warming of the coronary sinus area through the wall of the coronary vein or inferior caval vein in the dog heart in situ.

Since an electrocardiogram with three limb leads obtained in such an experiment has never been reproduced to our knowledge, one of these experiments may be described here. Fig. 5 was obtained from a dog weighing 4.45 kilograms. During artificial respiration, the chest wall and pericardium were opened under nembutal and morphine anesthesia. The apical area of the heart was slightly lifted from its pericardial bed and a thermode was applied through the wall of the inferior caval vein to the area around the orifice of the coronary sinus.

Lead I, obtained after discontinuation of the warming of the coronary sinus, shows in the beginning a tachycardia caused by the warming of the coronary sinus area. The P waves are not clearly visible because they are low. With slowing of the heart rate, sinus rhythm with normal positive P waves recurs. Lead II, registered during the tachycardia, shows deeply inverted P waves followed by positive Ta waves and preceding the QRS complex by about 0.11 second. The tracing of Lead III, as in Lead I, was obtained after discontinuation of the warming process. In the first half of the tracing, deeply inverted P waves precede the QRS complex, but in the second half regular sinus rhythm recurs with high positive P waves and inverted Ta waves.

In all experiments, the same pattern of P waves was obtained as in the clinical tracings. In Lead I the P wave was invisible or low positive; in Leads II and III it was deeply inverted and usually sharply peaked.

In our opinion, coronary sinus rhythm is actually not as rare as it is often believed to be; then too, it is frequently overlooked. That inverted P waves appear under normal conditions in Lead III is known but when they were also found in Lead II, they were often not attributed to a new rhythm but rather explained by summation according to the Einthoven rule. Some authorities[7] diagnose auriculoventricular rhythm even with isoelectric P waves in Lead II. For this study we accepted only cases with definitely inverted P waves in Leads II and III. In doubtful cases it will be of help to know that coronary sinus rhythm is extremely variable and that spontaneously, or with carotid pressure, or exercise, it changes readily into sinus rhythm.

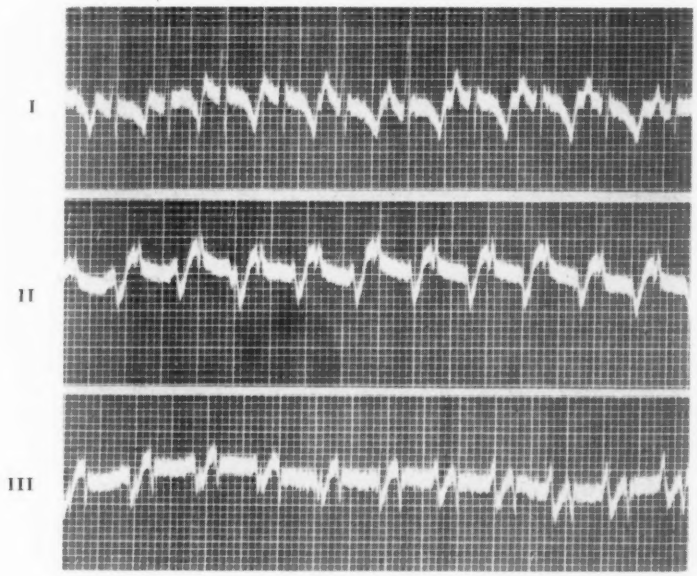

Fig. 5.—Coronary sinus rhythm produced experimentally in the dog. For description of the three limb leads, see text.

Only twice during the observation period of six years did we find the form of auriculoventricular rhythm with inverted P waves between QRS and T; that is, auriculoventricular rhythm originating in the lower node. Both times, this rhythm was temporary. Auriculoventricular rhythm without visible P waves, usually attributed to a stimulus originating in the middle of the auriculoventricular node, was seen only nine times. These results differ from those of other writers[20] who saw among 45 patients with auriculoventricular rhythm the merging of P waves with QRS complexes in twenty-four instances.

Since it is known that the automaticity of the specific fibers of the heart diminishes gradually from above downward,[8] one would expect that the coronary sinus area, in view of the high automaticity of the coronary sinus fibers, is always next in line if the sinus node ceases to function and that this form of auriculo-

ventricular rhythm would occur more often. Actually, even in animal experiments which are more susceptible to analysis, the destruction of the sinus node is frequently followed by that form of auriculoventricular rhythm in which the auricle and ventricle contract simultaneously and not by coronary sinus rhythm as one might expect.

The fact that the coronary sinus area is in such close contact with nerve fibers and ganglion cells, and is so easily influenced by exercise, carotid pressure, and other factors, appears to us to offer the explanation. Since the vagus nerve exerts a greater chronotropic effect on the coronary sinus region than on the main part of the auriculoventricular node,[8] it is clear that every factor which abolishes the action of the sinus node by vagal effects, such as carotid sinus pressure, digitalis, and reflexes,[22] may also lead to inhibition of the activity of the coronary sinus. Under these circumstances, the pacemaker will be situated in the deeper parts of the auriculoventricular node, and both auricle and ventricle will be activated simultaneously. Moreover, even with stimulus formation in the coronary sinus area, the reversed conduction to the auricle may be prevented by a high vagal tonus so that electrocardiograms of these two forms would look alike.

Blocking of the reversed conduction to the auricle is the most probable reason why warming of the coronary sinus area in experiments on the Langendorff heart caused a rapid auriculoventricular rhythm without causing the P waves to become visible before the QRS complexes.[23] In such experiments, naturally normal conditions never prevail. It has been claimed that crushing of the specific fibers of the sinus node, thus abolishing its activity by strong stimuli, causes auriculoventricular rhythm with a positive P-R interval while stopping the activity of the sinus node by cooling leads to auriculoventricular rhythm in which auricle and ventricle contract simultaneously.[4] These results were not confirmed.[23]

Some confusion was introduced into the picture when some authors[3,10,13] called electrocardiograms with positive P waves in each lead and P-R intervals of 0.12 second or less coronary sinus or coronary nodal rhythm. Such tracings, however, belong to a normal sinus mechanism,[26] and the short P-R interval must be attributed to other causes. It is frequently found in thiamine deficiency and is often seen in certain types of hypertension.[25] A shortened P-R interval with positive P waves and abnormal ventricular complexes is also seen in the Wolff-Parkinson-White syndrome, which is explained by an abnormal connection between auricle and ventricle.

The question arises as to whether or not one is justified in separating coronary sinus rhythm from the rhythm originating in the auricuiar portion of the auriculoventricular node. According to some authorities, definite shortening of the P-R interval would speak for upper auriculoventricular nodal rhythm while a normal P-R interval would permit the diagnosis of coronary sinus rhythm.[28] Table I shows, however, that the length of the P-R interval during coronary sinus rhythm will depend to a great degree on the length of the P-R interval during sinus rhythm in the respective patient. The P-R interval during coronary

sinus rhythm is often, but not always, slightly shorter than during regular sinus rhythm. With a P-R interval of 0.18 second during regular sinus rhythm, a P-R interval of 0.12 second or more may be found during coronary sinus rhythm. The condition of the auriculoventricular conduction system will influence the P-R interval during both rhythms.

In experimental work on dogs, the P-R interval during coronary sinus rhythm was shorter[8] or longer[30] than during sinus rhythm. In the latter instance, a very rapid heart rate usually prevailed which may explain the prolongation. In eight experiments on dogs, the length of the P-R interval during both rhythms was compared[24] and was not found shorter when sinus rhythm changed into coronary sinus rhythm. Here, however, the rate during coronary sinus rhythm was also rapid. It appears, therefore, that until more is known about this rhythm, the question of separation of the coronary sinus rhythm from the "upper nodal rhythm" must be left open since the borderline between them is still not sharply defined.

Since the term, coronary sinus rhythm, may easily be confused with sinus rhythm, the problem arises as to whether another designation for the rhythm originating around the coronary sinus may not be preferable. Supranodal rhythm, a term proposed for the auriculoventricular rhythm in which the P wave precedes the QRS complex in a normal interval,[5] may be considered as a possible synonym.

While coronary sinus rhythm is usually found in an abnormal heart, particularly in patients with coronary sclerosis and hypertension, it may occur in an otherwise apparently healthy person. A slight depression of the activity of the sinus node and a moderate acceleration of the coronary sinus centers may cause the abnormal rhythm.

CONCLUSIONS

Electrocardiographic and clinical observations made on thirty-one patients with coronary sinus rhythm are discussed.

Coronary sinus rhythm has a well-defined electrocardiographic picture with a normal or slightly shortened P-R interval, low positive or absent P waves in Lead I, and deep, inverted P waves, which are usually peaked, in Leads II and III.

A large majority of patients demonstrating this disturbance have evidence of an organic heart lesion.

The anatomic and physiologic peculiarities of the specific tissue around the orifice of the coronary sinus vein are discussed.

Differentiation between the rhythm originating in the area of the coronary sinus and the rhythm originating in the upper part of the auriculoventricular node is not yet possible.

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ABNORMALITIES OF THE RESPIRATORY PATTERN IN PATIENTS WITH CARDIAC DYSPNEA

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INTRODUCTION

DETAILED analyses of the time relationships and variations in contour of respiratory tracings recorded by the Marey pneumograph have not been made in patients with cardiac dyspnea. Spirographic records of respiration in patients with dyspnea due to heart disease have been concerned only with rate and depth of breathing and not with variations in the relative duration of expiration and inspiration or with changes in form. Furthermore, since spirographic tracings employ a slowly moving cylinder, the records are closely compressed so that variations in contour are not easily detected, and accurate measurements of time relationships are difficult. By utilizing a rapidly moving drum, the pneumograph yields tracings which can easily be measured. The present study deals with an analysis of the time relationships of expiration and inspiration and of changes in contour recorded by such means. Observations were made on normal subjects as well as on patients with cardiac dyspnea and dyspnea due to allergic bronchial asthma. The changes produced by exercise and by the administration of aminophylline were also noted.

METHOD OF STUDY

A record of the chest movements during breathing were made with a Marey pneumograph which produced tracings on smoked paper on the rotating drum of a kymograph. Measurements were made by means of a caliper micrometer of (a) the total duration of individual breaths, (b) the duration of inspiration, and (c) the duration of expiration. The estimated respiratory rate for each breath was computed from the total duration of that cycle. Many breaths were thus measured at various intervals on each record. The value for the respiratory rate, the durations of inspiration and expiration in each breath, plus the numerical ratio of duration of expiration (in seconds): duration of inspiration (in seconds) were then expressed for each tracing. By this method of study, observations were made on normal subjects, patients with dyspnea and pulmonary congestion caused by heart failure, and patients with allergic bronchial asthma. Studies of the vital capacity were also made before and after administration of aminophylline (theophylline ethylenediamine) intravenously. The five normal subjects studied were medical students ranging in age from 20 to 25 years. They were free of any clinical evidence of cardiac or pulmonary disease; determinations of the circulation time (employing ether and decholin) and venous pressure were made and were found to be normal. Eleven patients with heart disease, ranging in age from 22 to 79 years, who were free of any history of allergic manifestations were studied (see Table I). Three of these patients suffered from syphilitic aortic insufficiency, four were diag-

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nosed as having hypertensive heart disease and two as having arteriosclerotic heart disease, and two revealed evidence of mitral stenosis of rheumatic origin. All of these eleven subjects showed clinical and roentgenologic evidence of pulmonary congestion, with moist râles in the lung fields and, in several cases, with a definite wheezing type of expiration. All tracings were taken in the sitting position. The exercise in normal subjects consisted of forward bending from a standing position, touching the toes with the fingers forty times. In the patients with heart disease, a few were able to bend forward and touch the toes ten times, while in the remainder, swinging of the arms across the chest from ten to sixty times (depending on the capacity of the individual patient for exercise) was sufficient to produce a definite hyperpnea.

RESULTS

Normal Subjects at Rest.—In Fig. 1, *A*, is shown a typical tracing of a normal subject at rest. The great majority of tracings revealed a similarity of contour for each individual subject and the shape of the tracing tended to reproduce itself in the same patient, with some minor deviations. The inspiratory downstroke was typically very slightly concave and the expiratory upstroke very slightly convex (upward). The inspiratory phase tended to follow immediately after expiration without pause. The infrequency of the expiratory pause has been previously noted in an analysis of spirographic tracings by Caughey.[1] The total duration of each individual breath varied inversely with the respiratory rate, being shorter with a rapid rate and longer with a slow respiratory rate. The numerical relationship of the duration of expiration (in seconds) to the duration of inspiration (in seconds) varied, for the five subjects at rest, from 1.30:1 to 1.96:1 (Fig. 2). The average value for the expiratory: inspiratory ratio in the five normal subjects at rest was 1.61. Otherwise stated, this means that the average duration of expiration was 1.61 times as long as the average value for inspiration in these normal subjects. This is in close agreement with values found for this ratio by Mudd[2] by means of spirographic tracings.

Normal Subjects After Exercise.—Reference to Fig. 3*A* shows that after exercise the respiratory rate increased sharply and the duration of inspiration decreased somewhat, while the duration of expiration fell sharply. This decrease in the duration of expiration following exercise was of much greater magnitude than the decrease in the duration of inspiration. Fig. 3*B* reveals that the ratio, duration of expiration: duration of inspiration, also fell abruptly in the cycles immediately following exercise. After the subject recovered from his hyperpnea the duration of inspiration, expiration, and the expiratory: inspiratory ratio slowly returned toward resting values. The changes seen in Figs. 3*A* and 3*B* were found to be a constant pattern recurring after exercise in all of the five normal subjects. Reference to Fig. 2 will show that the average expiratory: inspiratory ratio for the group of normal subjects immediately after exercise was found to be 1.39:1. It will be seen from these data that the typical response to exercise in the normal subject was a selective shortening of the expiratory phase, and that it was mainly by shortening of this portion of each breath that the increase in respiratory rate occurred. The ease with which this change occurred indicated that there was, after exercise, both active participation of the muscles of expiration and an absence of any expiratory obstruction.

Patients With Heart Disease: *Studies While Resting.*—In Fig. 1, *C* and *D*, is shown a definite lengthening of the expiratory phase in resting patients with cardiac dyspnea. The tracings also were typified by an increase in upward convexity of the expiratory limb. The *relative* duration of the expiratory phase was

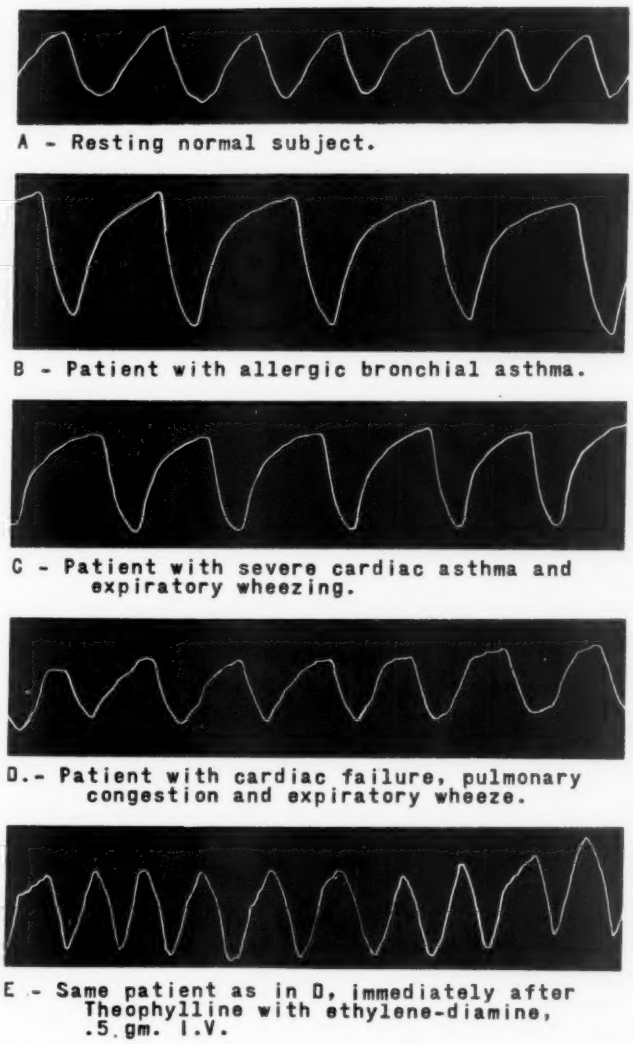

Fig. 1—Pneumographic tracings. Downstroke, inspiration; upstroke, expiration.

found to be considerably increased in all eleven patients with heart disease studied. Reference to Fig. 2 reveals that at rest the expiratory:inspiratory ratio gave definitely higher values than in the group of normal subjects. For the entire group the average expiratory:inspiratory ratio was found to be 2.17:1, with a range extending from 1.52 to 2.90. In any given patient, although fluctua-

tions occurred, the values were always found to fall in this range. This prolongation of the expiratory phase, with upward convexity of the expiratory limb, was most striking in the patients with frank cardiac asthma (Patients 1, 3, 4, and 7, Table I, and Patient *C*, Fig. 1) but was also seen in the other patients with heart disease who were free of the expiratory wheeze. These studies were interpreted as indicating that there is a definite relative prolongation of expiration in the patient suffering from cardiac dyspnea.

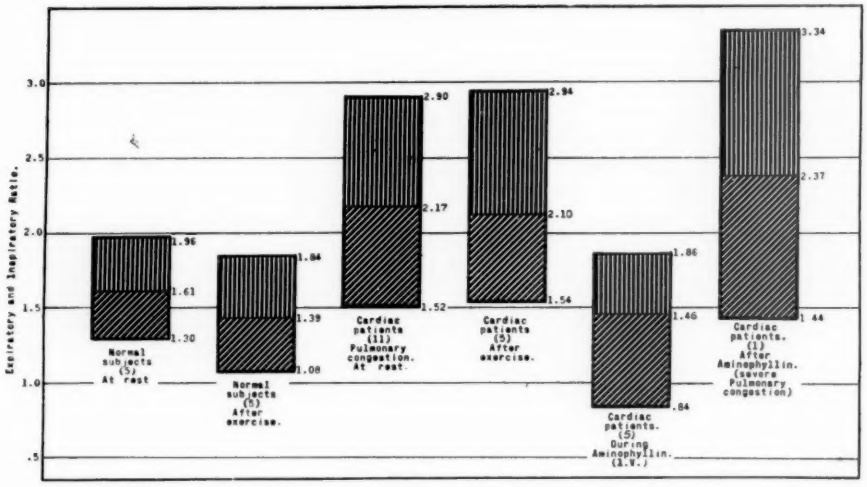

Fig. 2.—Expiratory:inspiratory ratio in normal subjects and patients with heart disease. Middle figure, mean for group; upper and lower figures, maximum and minimum range for group.

TABLE I. EXPIRATORY:INSPIRATORY RATIO OF PATIENTS WITH HEART DISEASE

PATIENT	DIAGNOSIS	AVERAGE EXPIRATORY:INSPIRATORY RATIO		
		AT REST	AFTER EXERCISE	AFTER AMINOPHYLLINE
1 (J. H.)	Syphilitic aortic insufficiency; cardiac asthma	2.69	2.54	1.56
2 (C. M.)	Hypertensive heart disease	1.94	1.77	1.26
3 (C. W.)	Rheumatic heart disease; mitral stenosis; cardiac asthma	2.03	2 18	1.60
4 (M. Y.)	Hypertensive heart disease; cardiac asthma	2.38	2.00	—
5 (F. C.)	Syphilitic aortic insufficiency	2.00	—	1.55
6 (G. S.)	Hypertensive heart disease	2.03	2.00	1.50
7 (G. P.)	Hypertensive heart disease; cardiac asthma	2.24	—	—
8 (J. J.)	Arteriosclerotic heart disease	2.07	—	—
9 (M. G.)	Arteriosclerotic heart disease	2.12	—	—
10 (M. J.)	Rheumatic heart disease; mitral stenosis	1.96	—	—
11 (W. L.)	Syphilitic aortic insufficiency	2.30	—	—
Average expiratory:inspiratory ratio		2.17	2.10	1.46

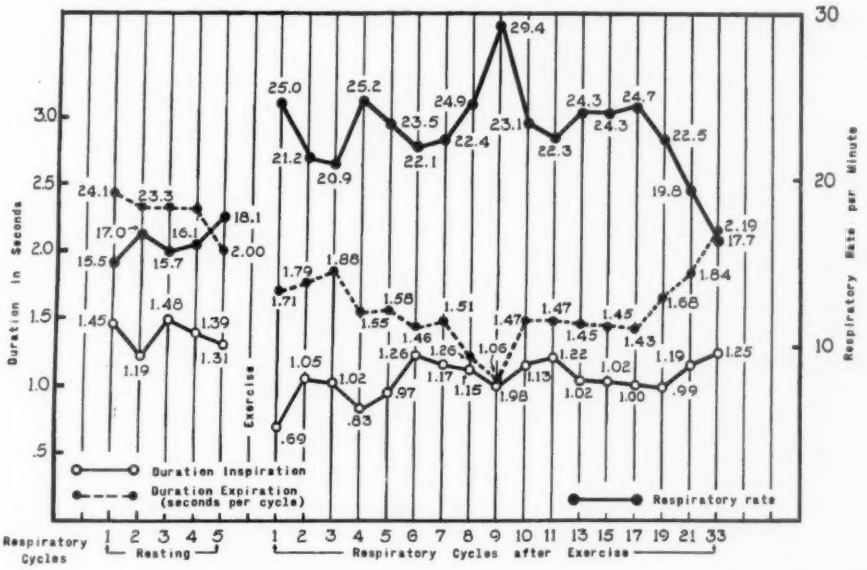

Fig. 3*A*.—Actual duration of expiration and inspiration (in seconds) per breath in normal subject (M. B.) at rest and after exercise.

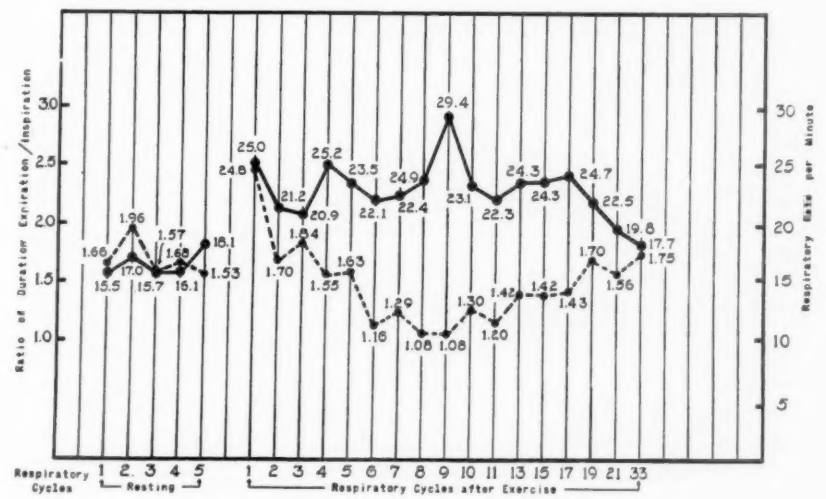

Fig. 3*B*.—Expiratory: inspiratory ratio for individual breaths of normal subject (M. B.) at rest and after exercise (same patient as in Fig. 3*A*).

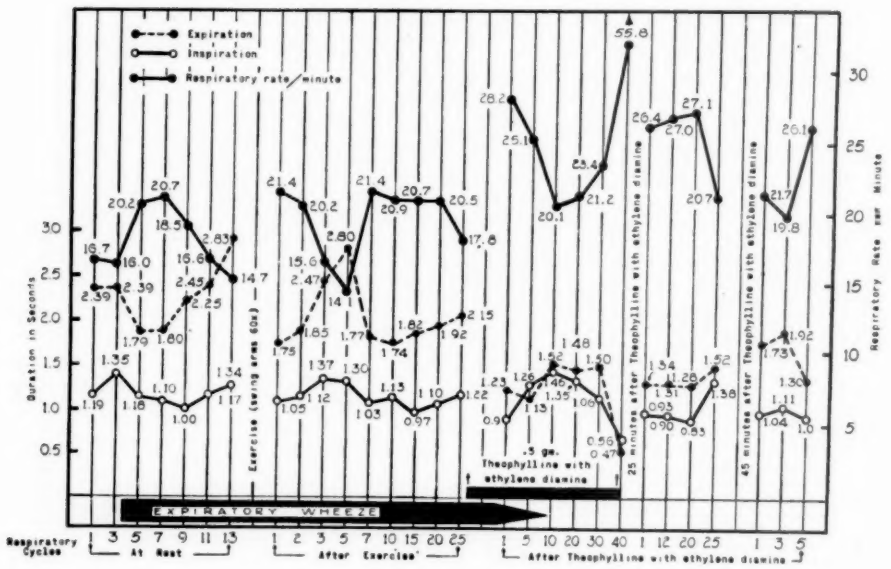

Fig. 4*A*.—Actual duration of expiration and inspiration (in seconds) per breath in patient with heart disease at rest, after exercise and after administration of aminophylline. (Patient C. M.)

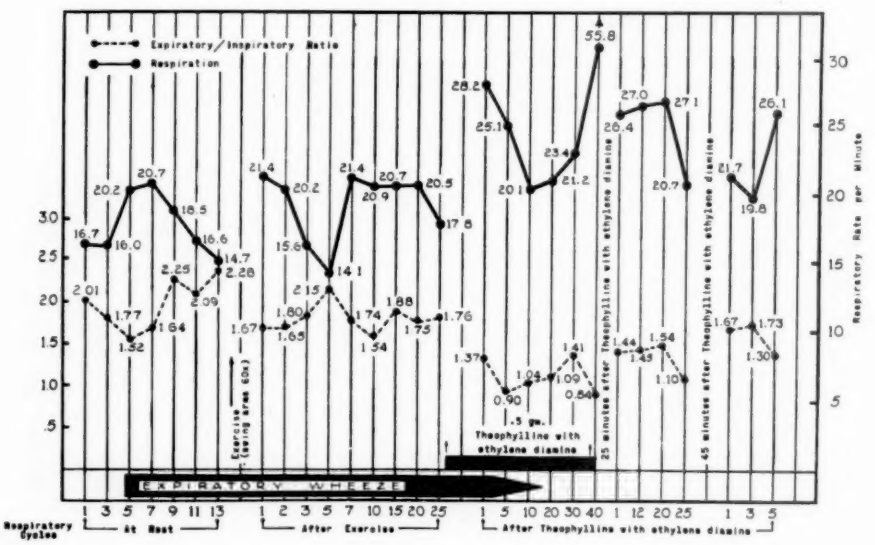

Fig. 4*B*.—Expiratory: inspiratory ratio for individual breaths in patient with heart disease at rest, after exercise, and after administration of aminophylline (same patient as in Fig. 4*A*).

Patients With Cardiac Dyspnea: Studies After Exercise.—After an amount of exercise which was capable of producing a perceptible hyperpnea in patients with heart disease, the same type of observations were made. Reference to Figs. 4*A* and 4*B* reveals that, although there was an increase in respiratory rate after exercise and a slight shortening of inspiration and expiration, this shortening was proportionately the same for both phases of each respiratory cycle. The selective shortening of expiration which was seen in normal subjects did not occur in the patient with dyspnea, or occurred to a much less pronounced degree. Careful observation of the patients with heart disease also revealed that after exercise the accessory muscles of both expiration and inspiration were utilized to a much greater degree than in normal subjects. Likewise, the expiratory: inspiratory ratio remained at about the resting level, or decreased only slightly in this group, as shown in Fig. 2. These findings were interpreted to indicate that under ordinary conditions the cardiac patients were not capable of the selective shortening of the expiratory phase which was exhibited in normal subjects.

Patients With Asthma.—Two subjects with allergic bronchial asthma who revealed prolonged wheezing expiration on ausculation were studied, and in each case there was found to be a marked prolongation of the expiratory phase, with a marked upward convexity of the expiratory limb (Fig. 1, *B*). The average expiratory:inspiratory ratio for these two patients at rest was found to be 2.14. Since these subjects were presumed to have had active bronchospasm, this was confirmatory proof of the presence of obstructive expiratory dyspnea. After an amount of exercise (forward bending to touch toes) capable of producing marked dyspnea, the average expiratory:inspiratory ratio was found to be 1.81. There was thus a slight shortening of the expiratory phase, but definitely not to the same degree as in the normal subjects. After the administration of 0.5 Gm. of aminophylline, intravenously, the expiratory:inspiratory ratio revealed an average value for the two subjects of 1.67, and measurements revealed a definite shortening of the expiratory phase. Furthermore, determinations of vital capacity in the patients with asthma revealed abrupt increases of considerable magnitude (Fig. 5) immediately after the drug. It was observed that expiration occurred with much greater ease after this medication was administered.

Patients With Cardiac Dyspnea After Administration of Aminophylline.—Figs. 4*A* and 4*B* reveal that after the administration of aminophylline there was a marked relative shortening of the expiratory phase. Examination of the tracings obtained during the administration of this drug also revealed a marked change in contour (Fig. 1, *D* and *E*) with a sharp and rapid expiration. In the majority of cases, the decrease in duration of expiration began within a few seconds after the intravenous injection of the drug was started. Six patients with heart disease were given aminophylline. Five patients showed a selective shortening of the expiratory phase with an average expiratory: inspiratory ratio of 1.46 during the intravenous administration of the drug. In comparison with the normal group (Fig. 2) it will be noted that this approaches the value for the same ratio determined after exercise in normal subjects. In each case there was a precipitous rise in the respiratory rate after the drug, which was considered to be of central

origin. This selective shortening of expiration which occurred after the administration of aminophylline was the more remarkable in that acceleration of the respiratory rate after exercise in patients with heart disease had failed to produce such a relative shortening. The vital capacity was measured before and immediately after the administration of aminophylline in five of the patients with cardiac dyspnea. Reference to Fig. 5 reveals that whereas in a normal subject the increase in vital capacity was insignificant, there was a definite increase in vital capacity (ranging from 150 to 800 c.c.) in the patients with heart disease (Table II). Since these increases occurred within periods of four to six minutes after

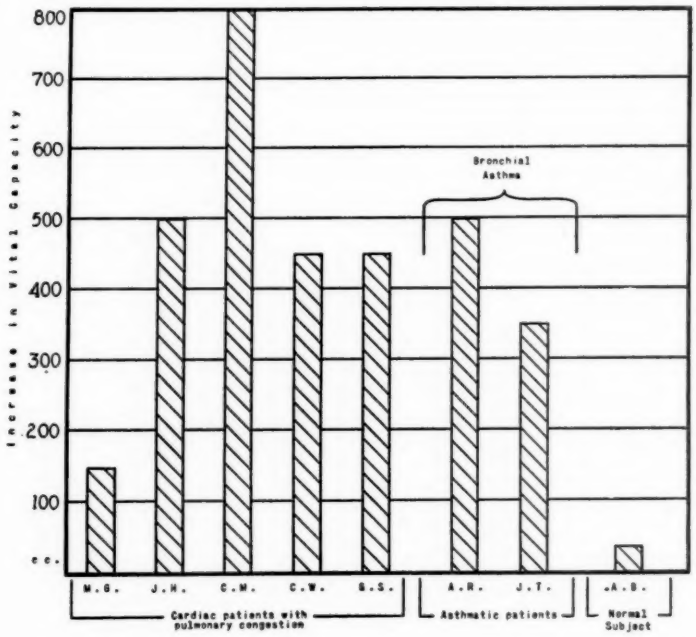

Fig. 5.—Increases in vital capacity after administration of aminophylline, 0.5 Gm. intravenously, in patients with heart disease, patients with bronchial asthma, and in a normal subject.

the beginning of the administration of the drug, and since moist râles were still present on auscultation and x-ray films of the chest showed the persistence of pulmonary congestion, the conclusion that there had been partial or complete abolition of variable degrees of bronchospasm seemed warranted. This was further supported by the fact that on auscultation of the chest of two of these patients who suffered from cardiac asthma, there was a prompt disappearance of expiratory, wheezing râles during the injection. Reference to Fig. 2 reveals that in the sixth subject, who suffered from very extreme pulmonary congestion, there was no alteration in the duration of expiration and the expiratory:inspiratory ratio after aminophylline. This was interpreted as indicating either that a severe degree of bronchospasm which was not relieved by the drug was present or that extreme pulmonary congestion had produced a leathery consistency of the lung with loss of normal elastic contractility.

TABLE II. VITAL CAPACITIES—PATIENTS WITH HEART DISEASE

PATIENT	AT REST (C.C.)	PREDICTED NORMAL (%)	AFTER AMINOPHYLLINE (C.C.)	INCREASE (C.C.)
1 (J. H.)	2,200	48	2,700	500
2 (C. M.)	2,600	79	3,400	800
3 (M. S.)	2,200	50	2,650	450
4 (C. W.)	1,900	43	2,350	450
5 (M. G.)	2,100	49	2,250	150

DISCUSSION

The normal subjects were capable of a marked increase in respiratory rate and depth after exercise without severe subjective symptoms of dyspnea. This increase in rate was accomplished mainly by a selective shortening of the duration of expiration. These changes occurred with ease, to meet the needs for increased ventilation, and there was no apparent obstruction in either inspiration or expiration. Further, in a normal subject given aminophylline intravenously, there was only an insignificant increase in vital capacity.

In patients with cardiac dyspnea, the striking factors noted were a relative prolongation of the expiratory phase at rest, and a failure of this phase to undergo relative shortening after exercise. This prolongation of the expiratory phase was most strikingly seen in patients suffering from "cardiac" asthma, in whom the expiratory distress was easily found on auscultation, as evidenced by a prolonged, wheezing type of expiration. The pneumographic tracings obtained in both the patients with allergic asthma and those with cardiac asthma gave patterns which were almost identical in appearance. In each case the expiratory phase was markedly prolonged and was seen to possess an upward convexity. Patients with allergic asthma have previously been shown to have a definite prolongation of the expiratory phase by measurement of spirographic tracings.[2] Although the remaining seven cardiac patients with pulmonary congestion did not show prolonged, wheezing expiration on physical examination, careful measurements of their pneumographic tracings did reveal a relative prolongation of the expiratory phase well above its relative duration as determined in the normal subjects. The shape of the expiratory tracing in this latter group was intermediate between the configurations obtained in the normal subject and those with cardiac asthma but was also characterized by a tendency toward upward convexity.

After the administration of aminophylline, there was a prompt shortening of the relative duration of the expiratory phase in patients with cardiac dyspnea and with allergic asthma. This was accompanied by a significant increase in the vital capacity of both groups. Such increases in vital capacity in allergic asthma after the administration of aminophylline were observed in 1937 by Greene, Paul, and Feller,[3] but data showing such increases do not appear to have been presented for patients with cardiac dyspnea, despite the wide usage of aminophylline in this condition.

Although the prolonged, wheezing expiration of cardiac asthma has long been recognized clinically, pneumographic tracings to confirm this prolongation of expiration have been lacking. Since both the cardiac patients with asthma and those without the asthmatic wheeze revealed a prolongation of the expiratory phase, and since both groups revealed a prompt decrease in relative duration of expiration after aminophylline, accompanied by a prompt rise in vital capacity, the assumption that bronchospasm was present in both groups seems justified. Since none of the patients with heart disease had any previous personal history of allergic manifestations, it seemed unlikely that the expiratory difficulty was due to allergy. The bronchospastic element observed probably has its origin from reflexes arising in the congested pulmonary tissues. This aspect of the problem needs further investigation.

SUMMARY

1. Pneumographic tracings of respiration revealed a similar type of distortion and prolongation of the expiratory phase in cardiac patients with pulmonary congestion and in patients with allergic asthma. Expiration in these patients did not undergo the relative shortening after exercise seen in normal subjects.

2. During the administration of aminophylline intravenously, the expiratory phase of the patients with heart disease and asthma shortened promptly. Determinations of vital capacity in both groups also revealed abrupt increases of considerable magnitude immediately after this drug.

3. The possibility that the changes observed in the patients with heart disease are due to reflex bronchospasm caused by pulmonary congestion is suggested.

The author wishes to express his gratitude to Dr. Tinsley R. Harrison for his suggestions and advice throughout this study.

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THE INFLUENCE OF AGE ON BLOOD PRESSURE

A Study of 5,331 White Male Subjects

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THE question as to whether or not a physiologic rise in normal blood pressure occurs with advancing age has not thus far been satisfactorily answered. Conflicting clinical and statistical interpretations moreover have led to a wide divergence of authoritative opinion as to what constitutes the upper limit of normal at different ages.

Within recent years the highest acceptable level of the systolic reading has been persistently lowered so that "100 plus the age" no longer finds favor even with those who employ the most liberal critera for this physiologic measurement. In the last fifteen years many authorities[1-5] have designated 140 mm. Hg as the ceiling level for normal systolic blood pressure irrespective of age. According to this view,[3] a systolic reading above 140 mm. "is just as abnormal in an old man as in a young one." On the other hand, it has been shown repeatedly that a relatively high percentage of normal persons in middle life and old age manifest levels in excess of this limit.[6-8] Indeed, one of us (H. I. R.)[8] found that 64 per cent of a group of one thousand elderly seamen would have been considered to have abnormally high blood pressure by this delimitation. Furthermore, if the upper level of normal systolic blood pressure had been lowered to 120 mm. Hg, as advocated by Robinson and Brucer,[9] only 13 per cent of this entire series would have qualified as normal. In distinct contrast with these findings in older male groups have been the observations of blood pressure levels in young male adults. Thus, various reports[10-12] indicate that only 1 to 3 per cent of Army examinees in World War II had systolic blood pressures in excess of 150.

White[13] has stated that under the excitement of the examination, 160 mm. might be acceptable as the upper limit of the systolic blood pressure, but he would not raise the diastolic level much, if any, above 90 millimeters. Nevertheless, a recent publication by White and associates[14] suggests that even transient elevation of the systolic blood pressure above 150 is significant as a forerunner of sustained hypertension. The same conclusion was reached in regard to diastolic levels above 90. The follow-up studies of Hines,[15] however, are not in accord with this view. This author noted that "in the group of patients who had systolic blood pressure of more than 140 mm. but diastolic blood pressure of less than

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85 mm., none had subsequent hypertension." It appeared to Hines that a diastolic reading of 85 mm. represents a critical level with respect to future hypertensive disease. The prognostic significance of transient elevation of the systolic blood pressure, therefore, does not yet seem clearly established.

In an endeavor to investigate further the relationship between age and blood pressure, we have studied an unselected group of merchant seamen, coastguardsmen, and civilian male subjects.

MATERIAL FOR STUDY

The blood pressure levels of 5331 white men between the ages of 40 and 95 years were analyzed. These subjects were observed at the U. S. Marine Hospital, Staten Island, the U. S. Public Health Service Dispensary, Washington, D. C., Sailors Snug Harbor, Staten Island, and the New York City Farm Colony, Staten Island. The latter two institutions were the source of most of the aged individuals. The subjects from the Marine Hospital were healthy merchant seamen and coastguardsmen chiefly in the fifth and sixth decades of life. The subjects from Sailors Snug Harbor were older, retired seamen in the seventh to tenth decades of life. An analysis of this group was previously reported by one of us (H.I. R.).[8] The subjects from the U. S. Public Health Service Dispensary were candidates for civil service appointments, while those from the New York City Farm Colony were an older group of civilians, unemployed, indigent, or incapacitated by the infirmities of senescence. A study of the latter group has also been reported by one of us (I. M.)[6] In all instances, two or more blood pressure readings were taken. In the younger subjects an attempt was made to minimize the effect of excitement by instituting a short period of rest between blood pressure readings and a friendly chat. The older subjects were accustomed to having their blood pressure measured during routine morning rounds. All of the subjects were ambulatory. The persons observed at the various institutions numbered as follows:

U. S. Marine Hospital	1,588
Sailors Snug Harbor	1,000
U. S. Public Health Service Dispensary	1,887
New York City Farm Colony	856
Total	5,331

RESULTS

Table I represents an analysis of average systolic and average diastolic blood pressure* by five- and ten-year intervals. It is observed that average systolic blood pressure and pulse pressure rise with advancing years. Average diastolic

*The level at the beginning of the fourth phase was taken as the diastolic blood pressure.

TABLE I. AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE OF MALE SUBJECTS 40 TO 95 YEARS OF AGE

AGE (YR.)	NUMBER OF CASES	AVERAGE SYSTOLIC BLOOD PRESSURE (MM. HG)	T*	AVERAGE DIASTOLIC BLOOD PRESSURE (MM. HG)	T	AVERAGE PULSE PRESSURE (MM. HG)
40 to 44	831	133.3 ± 0.57†		84.8 ± 0.37		48.5
45 to 49	809	137.0 ± 0.68	4.0	86.6 ± 0.36	1.0	50.4
50 to 54	767	138.9 ± 0.82	1.8	87.0 ± 0.42	0.6	51.9
55 to 59	647	142.4 ± 1.02	2.6	87.7 ± 0.57	1.0	54.7
60 to 64	566	147.7 ± 1.16	3.4	87.6 ± 0.60	0.0	60.1
65 to 69	558	154.2 ± 1.22	4.1	88.5 ± 0.67	0.9	65.7
70 to 74	402	155.1 ± 1.37	1.6	87.0 ± 0.72	1.4	68.1
75 to 79	370	160.6 ± 1.31	2.6	88.2 ± 0.88	1.1	72.4
80 to 84	255	160.4 ± 1.65	0.0	86.8 ± 0.95	1.1	73.6
85 to 95	126	164.0 ± 2.22	1.5	90.0 ± 1.26	1.5	74.0
40 to 49	1,640	135.1 ± 0.44		85.8 ± 0.27		49.3
50 to 59	1,414	140.8 ± 0.64	7.4	87.4 ± 0.35	3.7	53.4
60 to 69	1,124	150.8 ± 0.84	9.5	88.1 ± 0.50	1.2	62.7
70 to 79	772	158.6 ± 0.96	6.1	87.6 ± 0.57	0.5	71.0
80 to 95	381	161.7 ± 1.34	1.8	87.9 ± 0.78	0.5	73.8
40 to 59	3,054	138.5 ± 0.37		86.5 ± 0.21		52.0
60 to 95	2,277	153.9 ± 0.58	23.0	87.8 ± 0.32	3.2	66.1
40 to 95	5,331	144.7 ± 0.35		87.1 ± 0.18		57.6

*T, employed in this and Tables II, III, and IV, represents the number of times greater the observed difference between an average or proportion of one age group and that of the preceding age group is than the standard error of that difference.

†These values are standard errors.

blood pressure, on the other hand, increases only slightly with age, the largest increment occurring between the fifth and sixth decades. These trends are shown in Figs. 1 and 2.

Table II was constructed by calculating the percentage of persons in each age group having "normal" blood pressure (149/195 or less), systolic hypertension (systolic, 150 mm. or over; diastolic, 95 mm. or less), and diastolic hypertension (diastolic, 96 mm. or over). A steady and progressive decrease in the incidence of "normal" blood pressure occurs with advance of age, the fall being from 87.2 per cent in the 40- to 44-year age group to 27.8 per cent in the 85- to 95-year age group. In direct contrast, a marked increase is noted in the frequency of systolic hypertension, the change being from 4.2 per cent to 45.2 per cent in the same age interval. When diastolic hypertension is analyzed, the incidence is found to rise from 9.6 per cent in the fifth decade to 20.2 per cent in the seventh decade, remaining relatively unchanged thereafter. Fig. 3 graphically represents the variations with age in the incidence of "normal" blood pressure, systolic hypertension, and diastolic hypertension.

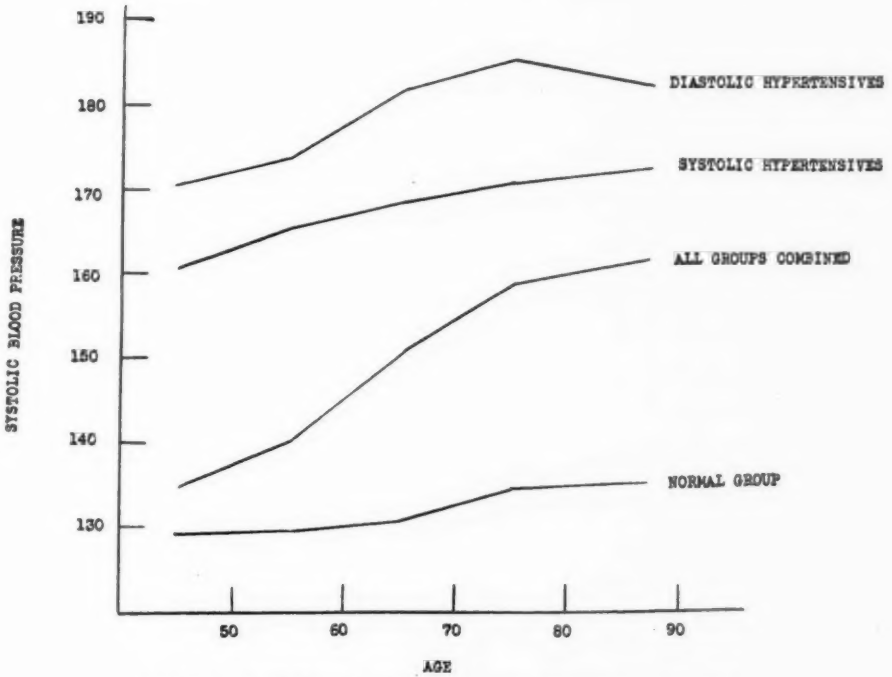

Fig. 1.—The relationship of age to average systolic blood pressure.

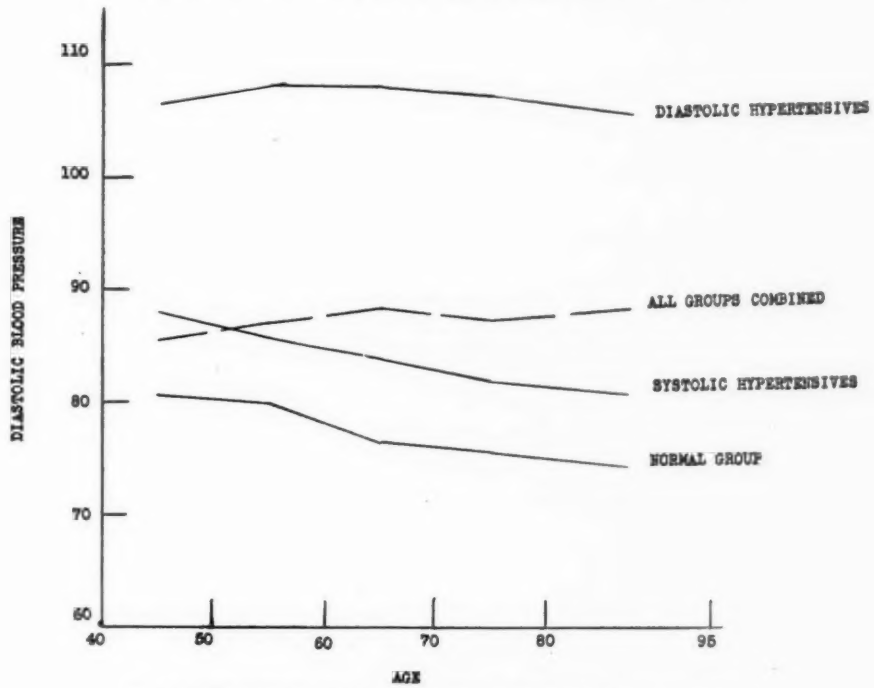

Fig. 2.—The relationship of age to average diastolic blood pressure.

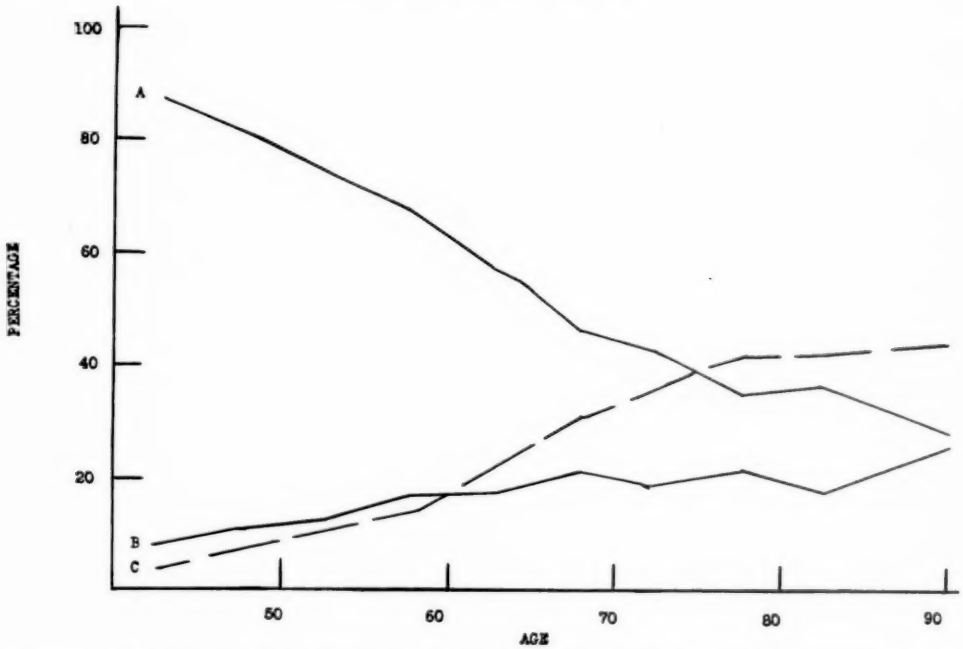

Fig. 3.—The relationship of age to percentage incidence of normal blood pressure (*A*), diastolic hypertension (*B*), and systolic hypertension (*C*).

TABLE II. PERCENTAGE INCIDENCE OF NORMAL BLOOD PRESSURE, SYSTOLIC HYPERTENSION, AND DIASTOLIC HYPERTENSION

AGE (YR.)	NORMAL BLOOD PRESSURE		SYSTOLIC HYPERTENSION		DIASTOLIC HYPERTENSION	
	%	T	%	T	%	T
40 to 44	87.2		4.2		8.5	
45 to 49	81.7	3.1	7.5	2.9	10.8	1.5
50 to 54	74.8	3.3	11.5	2.6	13.7	1.8
55 to 59	68.2	2.7	14.7	1.8	17.1	1.8
60 to 64	57.9	3.7	22.8	3 6	19.3	0.9
65 to 69	47.8	3.4	31.0	3.1	21.1	0.8
70 to 74	43.0	1.4	38.3	2.3	18.7	1.0
75 to 79	35.1	2.2	43.0	1.3	21.9	1.1
80 to 84	36.1	0.2	44.3	0.1	19.6	0.8
85 to 95	27.8	1.6	45.2	0.1	27.0	1.6
40 to 49	84.5		5.8		9.6	
50 to 59	71.8	8.4	12.9	6.7	15.3	4.7
60 to 69	52.9	9.9	26.9	8.7	20.2	3.2
70 to 79	39.2	6.0	40.5	6.1	20.2	0.0
80 to 95	33.3	2.0	44.6	3.6	22.0	0.7
40 to 59	78.6		9.1		12.3	
60 to 95	45.0	18.6	34.4	10.5	20.6	3.2
40 to 95	64.3		20.0		15.8	

TABLE III. "NORMAL" BLOOD PRESSURE GROUP

AGE (YR.)	NUMBER OF CASES	SYSTOLIC BLOOD PRESSURE AVERAGE (MM.)	T	DIASTOLIC BLOOD PRESSURE AVERAGE (MM.)	T	PULSE PRESSURE AVERAGE (MM.)
40 to 49	1,386	129.6 ± 0.28		80.9 ± 0.20		48.7
50 to 59	1,015	129.6 ± 0.38	0.0	80.1 ± 0.26	2.5	49.5
60 to 69	595	130.2 ± 0.55	0.9	76.8 ± 0.39	7.4	53.4
70 to 79	303	133.7 ± 0.87	3.4	75.7 ± 0.60	1.5	58.0
80 to 95	127	134.1 ± 1.0	0.3	74.5 ± 0.93	1.0	59.6
40 to 59	2,401	129.6 ± 0.24		80.6 ± 0.16		49.0
60 to 95	1,025	131.7 ± 0.40	4.5	76.2 ± 0.30	13.3	55.5
40 to 95	3,426	130.3 ± 0.20		79.2 ± 0.15		51.1

AGE (YR.)	SYSTOLIC BLOOD PRESSURE 140-149 MM.		DIASTOLIC BLOOD PRESSURE 90-95 MM.		DIASTOLIC BLOOD PRESSURE BELOW 70 MM.		120/80 OR LESS	
	%	T	%	T	%	T	%	T
40 to 49	18.6		15.4		3.6		27.5	
50 to 59	24.4	2.0	14.4	0.7	6.4	3.0	29.0	0.8
60 to 69	28.2	3.0	12.2	1.3	15.1	5.2	32.1	1.3
70 to 79	36.3	2.4	15.1	1.5	20.1	1.7	26.0	1.9
80 to 95	40.9	0.9	15.7	0.2	21.2	0.3	26.7	0.0
40 to 59	19.8		15.0		4.7		28.1	
60 to 95	32.1	7.2	13.5	1.1	16.5	9.5	29.7	1.1
40 to 95	23.5		14.6		8.5		28.6	

The trends of "normal" systolic and "normal" diastolic blood pressure are analyzed with respect to age in Table III. Average "normal" systolic pressure tends to increase progressively from 129.6 mm. in the 40- to 49-year age group to 134.1 mm. in the 80- to 95-year age group. Comparison of average "normal" systolic pressure in the age period 40 to 59 with that in the age period 60 to 95 shows a significantly higher level in the older group. Average "normal" diastolic pressure tends to decrease progressively from 80.9 mm. in the 40- to 49-year age group to 74.5 mm. in the 80- to 95-year age group. The incidence of blood pressures of 120/80 or less shows no significant change with advancing years. In sharp contrast, one observes a significant rise with age in the frequency of systolic blood pressures between 140 and 149 millimeters. There is also an increasing incidence of diastolic blood pressures below 70. The frequency of diastolic pressures over 90 mm., on the other hand, is not altered in the "normal" group with succeeding decades. It appears, therefore, that the trend of normal systolic blood pressure with age is upward, while that of normal diastolic blood pressure is downward. If the rise in "normal" systolic pressure were due solely

TABLE IV. AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE OF MALE SUBJECTS WITH SYSTOLIC AND DIASTOLIC HYPERTENSION

AGE (YR.)	AVERAGE SYSTOLIC BLOOD PRESSURE					AVERAGE DISATOLIC BLOOD PRESSURE			
	SYSTOLIC HYPERTENSION		DIASTOLIC HYPERTENSION			SYSTOLIC HYPERTENSION		DIASTOLIC HYPERTENSION	
	MM. HG	T*	MM. HG	T*	T†	MM. HG	T*	MM. HG	T*
40 to 49	160.8		168.4			87.7		106.9	
50 to 59	164.8		175.9			85.9		108.5	
60 to 69	168.0		182.1			83.7		107.9	
70 to 79	168.9		186.8			81.9		107.3	
80 to 95	171.9		182.5			81.5		105.6	
40 to 59	163.4 ± 0.78		171.9 ± 1.27		5	86.6 ± 0.60		107.8 ± 0.52	
60 to 95	169.1 ± 0.53	6.4	184.7 ± 1.13	7.6	10	82.5 ± 0.35	5.6	107.3 ± 0.44	0.7
40 to 95	167.6 ± 0.44		179.7 ± 0.89		12	83.6 ± 0.39		107.5 + 0.38	

*Refers to values between 40- 50-year age group and 60- 95-year age group.
†Refers to values comparing subjects with systolic hypertension with those with diastolic hypertension within the same age group.

to potential hypertension in the "normal" group, an associated rise in "normal" diastolic pressure should be demonstrable. This, however, is not found. On the contrary, average "normal" diastolic pressure actually falls with age and there is, correspondingly, a progressive increase in the percentage of subjects with low levels of normal.

Our studies indicate that the average systolic blood pressure of each of the groups, "normal," systolic hypertensive, and diastolic hypertensive, increases significantly with advance of age. With respect to diastolic blood pressure, the averages for both "normals" and subjects with systolic hypertension decrease with age, while the average diastolic blood pressure for subjects with diastolic hypertension remains unchanged (Tables III and IV). Since in none of these individual blood pressure groups does the average diastolic pressure rise with age, the question may be raised as to why it shows this tendency when the entire group is considered as a whole. The answer undoubtedly lies in the rising incidence of diastolic hypertension with advancing age, a factor tending to elevate the average pressure of the combined groups. The trends in average systolic and average diastolic blood pressure for each of the blood pressure groups as well as for the total series is shown in Figs. 1 and 2, respectively.

DISCUSSION

Increase in average blood pressure with age does not constitute proof of a physiologic rise in normal blood pressure, for it is obvious that the hypertensive levels in the total population may distort the true picture of normal blood pressure trends. Robinson and Brucer, using 140/90 as the upper limit of normal, reported no increase in the mean arterial blood pressure with advancing years and thus concluded that normal blood pressure remains constant throughout life. Our examination of their data, however, does not uphold this view, for we discovered a significant rise with age in the incidence of systolic blood pressures in their upper range of "normal" (130 to 139 mm.). Furthermore, although these authors contended that the conclusions from their analysis would have been the same if the level of delimitation had been placed at 150 systolic and 95 diastolic, we have found, employing these ceiling values for normal in our series, that there is a tendency for normal systolic blood pressure to rise with advance of age (Table III). Moreover, if this increase were due chiefly to the presence of potential or latent hypertension in the "normal" group as alleged by these authors, a concomitant rise in diastolic blood pressure would also have been evident. Actually, however, a decrease rather than increase in "normal" diastolic pressure is observed with advance of age. We noted that the frequency of upper levels of "normal" diastolic blood pressure (90 to 95 mm.) remains unchanged when successively older groups are analyzed. On the other hand, the percentage of persons with systolic pressures in the upper range of "normal" (140 to 149 mm.), as well as the percentage with diastolic pressures in the lower range of normal (below 70 mm.), increase appreciably. Robinson and Brucer similarly found a rising incidence of low diastolic levels after the age of 55 years but admitted

that they "have not adequately accounted for this variation." The findings strongly suggest, therefore, that age exerts a definite influence on normal blood pressure, the systolic level rising and the diastolic level falling with advancing years. Why normal blood pressure is affected in this manner will now be considered.

Observations of various workers indicate that the physiologic process of aging influences all blood pressure levels through two major mechanisms, one neurogenic the other vascular. Russek[16] and Russek and Zohman,[17] using the cold-pressor test, have demonstrated that the reactibility of the blood pressure increases progressively as persons grow older. This increase in vasopressor response is attributed by Raab[18] to "increasing irritability of the cerebromedullary vasoconstrictor centers" with advancing years. The latter allegedly results from ischemia of the nerve centers controlling vascular tonus, a consequence of diminution in cerebral blood flow due to arteriolar sclerotic changes. That hypertension may actually arise from decreased cerebral blood flow is suggested by the recent experiments of Fishback and co-workers,[19] who were able to produce sustained elevation of the blood pressure in animals by ligating the arteries supplying the head. On the other hand, Dock[20] rejects the explanation that cerebral arteriosclerosis is responsible for increased vasomotor irritability and hypertension, declaring that these are rather the result of deterioration of the central nervous system with trophic loss of neurones associated with aging. Thus, vascular hyperreactibility and benign hypertension, in the opinion of Dock, are similar in origin to "senile intention tremor, Parkinsonism, and other involutional disorders of specific neurone groups." Whatever the explanation, evidence suggests that systolic and diastolic blood pressures are increasingly prone to transient elevation with advancing years. Although it has been maintained that a hyperreactive vascular system portends future hypertension, Russek and Zohman[17] found an increasing frequency of hyperreaction with age in subjects "unlikely to develop the disease" and even in those with hypotension. It seems possible, therefore, that other factors in addition to neurogenic vascular hyperreactibility are essential for the development of sustained hypertension. Sensitization of the vascular system by hormones from the adrenal cortex, adrenalin, angiotonin, or other substances, may be a necessary accompaniment. That a neurogenic mechanism is of importance in the pathogenesis of hypertension is reflected in the ability of caudal anesthesia[21,22] and lumbodorsal splanchnicectomy[23] to reduce hypertensive levels to normal in many cases. The neurogenic factor, therefore, appears to exert an influence tending to augment both systolic and diastolic blood pressure with advance of age.

A second mechanism, of purely vascular origin, also alters the blood pressure as one grows older. Diminution in the elasticity of the aorta and its large branches due to arteriosclerosis has been held responsible for the appearance of systolic hypertension in older groups. However, Herringham and Wills[24] and others have shown that the elasticity of arteries diminishes progressively with advancing years, becoming particularly marked with the fifth decade. Although loss of elasticity is frequently accepted as synonymous with ather-

osclerosis, it has been emphasized that many elderly persons have vessels with little eleasticity remaining but no atherosclerosis. Contrariwise, extensive sclerotic changes may be present even in young persons without significant loss of elasticity.[25] Normal vascular aging, therefore, appears to be reflected in a rising systolic pressure and falling diastolic pressure with advancing years. Systolic hypertension in the aged is undoubtedly a manifestation of the same vascular process. Considered in this light, these changes may be compared to the physiologic alterations occurring in the hair, skin, skeleton, and other structures with advancing years.

These considerations make it apparent that the neurogenic and vascular factors are summated in their influence upon systolic blood pressure while exerting opposing influences upon diastolic blood pressure. In normal persons and in those with systolic hypertension the vascular factor appears to dominate, as shown by a tendency of the average diastolic blood pressure to fall with age in each of the two groups. This change, however, is not observed in the group with diastolic hypertension.

Although only 9.1 per cent of the persons between 40 and 59 years had systolic hypertension, 34.4 per cent of the persons between 60 and 95 years manifested this type of blood pressure elevation. If it be accepted, therefore, that systolic blood pressure increases with age and that systolic hypertension is a normal finding in later life, the upper limit of normal systolic pressure for older groups must be elevated considerably above present-day standards. Indeed, the old dictum "100 plus the age" may yet regain its former prestige as an index of normal systolic blood pressure.

Acceptance of 140 mm. as the ceiling level for normal systolic blood pressure as advocated by others would have eliminated almost one-half (49.3 per cent) of our entire series. For the subjects between the ages of 60 and 95 years, 69.1 per cent would have been excluded by this limit. Furthermore, only 18.3 per cent of the entire series would have qualified as normal under the standards set by Robinson and Brucer (120/80 or less). Although 69.1 per cent of the persons between 60 and 95 years had systolic pressures of 140 mm. and over, only 41.9 per cent had diastolic pressures of 90 mm. and over. Hence, if these readings are employed as limits of normal, it is evident that there is a wide disparity in the "screening" value of the respective levels.

Most authorities accept small increments in the diastolic blood pressure with age as physiologic. We have pointed out, however, the tendency of normal diastolic blood pressure to fall rather than rise with age. It seems likely from studies of younger groups that normal diastolic blood pressure rarely exceeds 90.[13-15] If this is established, our observations would indicate that an even lower ceiling may be applicable to older age groups.

From these considerations it would appear that essential hypertension cannot be defined solely in terms of the systolic blood pressure, although this has been a common practice in earlier literature and even in some current literature. In general, our observations seem to support the views of Hines,[15] who, in his follow-up studies, noted that the diastolic pressure alone and not the systolic is of value in prognosticating the subsequent development of hypertension.

SUMMARY AND CONCLUSIONS

Although previous studies of unselected groups have demonstrated a progressive rise in *average* systolic and diastolic blood pressure with advancing years, no convincing proof has been offered that *normal* blood pressure increases physiologically with respect to age. Considerable difference of opinion exists, therefore, as to what constitutes the limits of normal at various periods of life.

A statistical analysis of the blood pressure levels of 5,331 white male subjects between the ages of 40 and 95 years is presented. The variations in blood pressure with age and the inferences drawn therefrom are as follows:

1. *Average* systolic blood pressure increases significantly with age, whereas *average* diastolic blood pressure shows little variation after the sixth decade.
2. The incidence of "normal" blood pressure (149/95 or less) falls markedly with age so that less than one-half (45.0 per cent) of the subjects 60 years old and older belong to this group.
3. The frequency of systolic hypertension rises sharply with advancing years. Approximately one-third (34.4 per cent) of the subjects 60 years of age and over show this type of blood pressure elevation.
4. The incidence of diastolic hypertension increases significantly up to the seventh decade, remaining relatively unchanged thereafter.
5. *Normal* systolic blood pressure tends to increase with age. The frequency of upper levels of "normal" (140 to 149 mm.) rises appreciably with advancing years.
6. The assumption that *normal* diastolic blood pressure increases with age is unfounded. Actually, a progressive decrease occurs with succeeding decades with the result that there is an increasing frequency of low diastolic levels (below 70 mm.) with advancing years.
7. The rise in normal systolic pressure and concomitant fall in normal diastolic pressure are primarily the result of progressive diminution in the elasticity of the aorta and its large branches associated with the process of aging (vascular factor).
8. The same physiologic mechanism is responsible for the increasing incidence of systolic hypertension which is merely the hemodynamic reflection of vascular aging.
9. Physiologic changes in the central nervous system leading to vascular hyperreactibility with advancing years similarly exert an important influence upon the blood pressure trends of all groups (neurogenic factor).
10. Both mechanisms (vascular and neurogenic) are summated in their effect upon systolic blood pressure while exerting opposing influences upon diastolic blood pressure.
11. The old maxim "100 plus the age" may actually be a fair index of normal systolic blood pressure.
12. Although the ceiling for normal diastolic blood pressure has been set at 90 mm. Hg, an even lower level appears applicable after middle age.
13. Essential hypertension cannot be defined solely in terms of the systolic blood pressure. It is the diastolic level alone that determines the existence of this disease.

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THE T WAVE OF THE PRECORDIAL ELECTROCARDIOGRAM AT DIFFERENT AGE LEVELS

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THIS paper is the first of a series dealing with the electrocardiographic study of 161 healthy Puerto Ricans. The subjects studied included 50 soldiers between 19 and 46 years of age; 31 women between the ages of 19 and 45 selected from the technical, nursing, and secretarial personnel of the University Hospital at San Juan, Puerto Rico; 20 young boys and 20 young girls ranging in age between 12 and 18 years; and 20 male and 20 female children between the ages of 5 and 11, most of them inmates of the Boys' and Girls' Charity Schools of our Insular Department of Health. All subjects were in an apparently normal state of health, with negative serologies, no histories of rheumatic arthritis, and no evidences of valvular heart lesion.

The standard leads were taken first in each case. Potential variations of the right arm (VR), the left arm (VL), the left leg (VF), and of the six precordial points were obtained by pairing an exploring electrode with a central terminal connected to the right arm, the left arm, and the left leg through a resistance of 5,000 ohms each. Wilson's central terminal with Goldberger's modification for augmented limb leads was used.

In taking the extremity and precordial leads, the connections of the galvanometer were so made that an upward deflection represented positivity of the exploring electrode and a downward deflection, negativity. The standard and extremity potentials were taken at normal sensitivity of the string (1 cm. = 1 mv.) and the precordial potentials at half normal sensitivity (1 cm. = 2 mv.). The six precordial points used were those specified by the Committee on Precordial Leads of the American and of the British Heart Association.[1] All tracings were made between 9 and 12 A. M. with the subjects in the reclining position.

We did not include older persons in our investigation, as the work of Willius,[2] Levitt,[3] Taran and Kaye,[4] Warnecke,[5] and Gelman and Brown[6] have proved conclusively that no less than 25 per cent of these subjects show distinct electrocardiographic abnormalities. Taran and Kaye, in their study of 102 men and women between 60 and 90 years of age, reported abnormal T waves in one-fourth of them. These findings were most commonly observed in the ninth decade and less often in the eighth, the most frequent finding being a negative T_4. Abnormal findings were as frequent in women as in men. The aged, therefore, cannot be considered normal individuals from a cardiovascular standpoint.

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Electrocardiographic studies of young adults have been performed by several investigators. We shall mention here Shanno,[7] who studied 100 student nurses of 18 to 22 years of age with the conventional leads and the precordial electrocardiograms CF_1 and CF_6; Larsen and Skúlason,[8] who analyzed the extremity deviations from 50 men and 50 women; Deeds and Barnes,[9] who studied

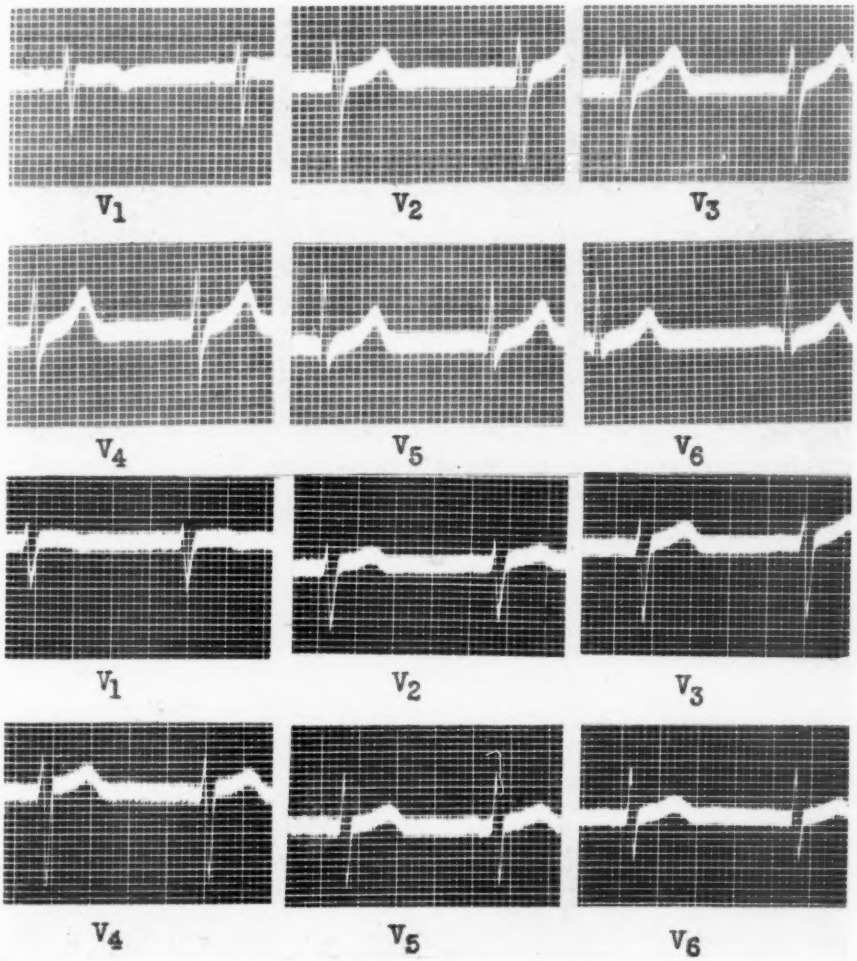

Fig. 1.—*A*, Case 776. P. R., aged 28 years, male. Negative T wave only in V_1. *B*, Case 787. M. H., aged 28 years, male. Negative T wave only in V_1. Both cases are typical of the electrocardiographic pattern of adult males.

the characteristics of the chest lead electrocardiograms of 100 normal adults and claim that CR is better than CL and CF. In one instance they found that the T wave approached negativity in Lead CF_2, but this never occurred in CR_2. Thomas[10] concludes that "until the limits of normal variation in the human electrocardiogram have been much more thoroughly explored, the diagnosis of heart

disease in young persons should seldom be based on electrocardiographic findings alone, in the absence of clinical manifestations." In an analysis of electrocardiograms obtained from 1,000 healthy aviators, Graybiel, McFarland, Gates, and Webster[11] utilized only the three standard leads and Lead IV F. In the latter they found that the T wave was upright in all but two instances, when it was

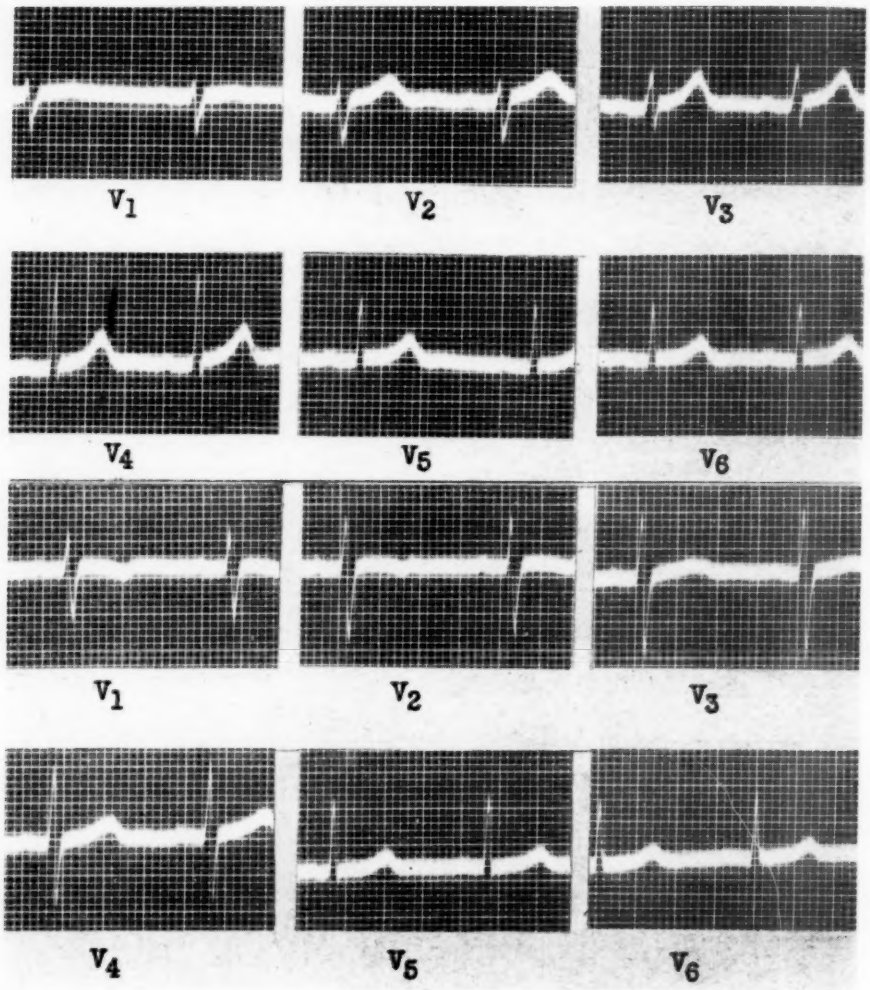

Fig. 2.—*A*, Case 812. A. Q., aged 28 years, female. No inverted T wave. *B*, Case 811. S. U., aged 19 years, female. Inverted T wave in V_1, diphasic in V_2.

diphasic. The range of the T wave was 1 to 15 mm. and the mean, 5.9 millimeter. Huge T waves, they state, are rarely observed in healthy persons. Kossman and Johnston[12] studied 30 subjects and published their table of normal values of the ventricular deflections for the standard and unipolar special leads.

Fetal electrocardiograms have rarely been taken with special apparatus,[13] and electrocardiographic studies in children have not been numerous. Lepeschkin[14] studied the normal chest electrocardiogram in 50 children from 2 weeks to 15 years of age. "The T wave," he says, "is inverted on the right chest anteriorly and upright on the left. On transition, a diphasic T is found. This transition is more to the left anteriorly in children than in grownups, and this deviation from the midline is greater the younger the child. These differences are related to the more lateral position of the interventricular groove in the younger child." Gelman and Brown[6] reported the electrocardiograms of 121 normal children between 12 and 14 years of age and compared them with a group of "normals" over the age of 61. These authors used only the three conventional leads.

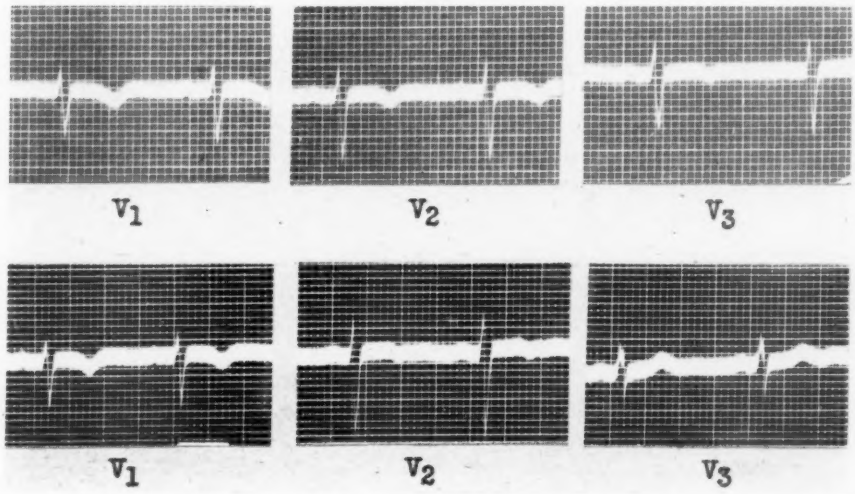

Fig. 3—Case 810. R. M. O., aged 20 years, female. Negative T wave in V_1, V_2, and V (upper row). Same subject a few days later, using identical technique and approximately the same precordial points, showed negative T wave only in V_1 and V_2 (lower row). In both instances heart was in semivertical position. A_{QRS} of + 58° in the first position and + 68° in the second.

Master, Dack, and Jaffe[15] studied the precordial leads in 71 normal children from 2 to 15 years of age. An upright or diphasic T wave to the left of the sternum, abnormal in adults, occurred in 60 per cent of the children. It was most frequent over the sternum, the incidence decreasing as the apex was approached, as in increasing age. No correlation was found between the shape of the heart or axis deviation and the presence of upright T waves. (The galvanometer connections were arranged so that upright deviations represented negative potentials.)

Groedel, Kisch, and Reichert[16] and Groedel and Miller[17] reported electrocardiographic studies in the newborn. These investigators, together with Kossman and Johnston, are the only one of the authors mentioned here, who have used the semidirect or unipolar leads. "While in the adults with normal heart

conditions," they say, "two different chest electrocardiograms—the left and the right—always exist, the newborn seem to show immediately after birth, usually over the whole thorax, only one pattern, that of the right chest electrocardiogram. This pattern changes in the left axillary line generally after a few hours, but

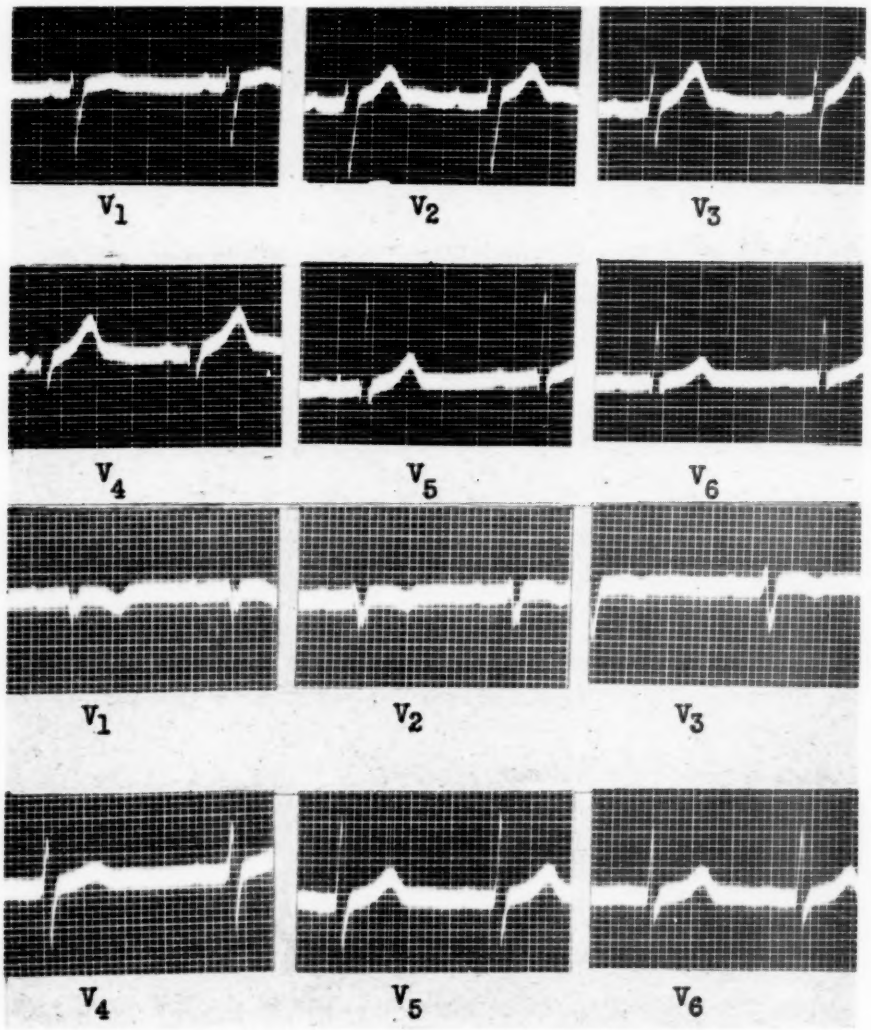

Fig. 4.—*A*, Case 986. M. V., aged 18 years, male. Adult type of electrocardiogram. Prolonged P-R interval in V_2, V_5, and V_6. *B*, Case 973. B. O., aged 15 years, male. Negative T wave in V_1, V_2, and V_3. Similar to child pattern, except for the relation of R height to S height.

not infrequently after days, into that of the left electrocardiogram. On the contrary, the chest electrocardiogram lead from the sternum does not change its character during the first life span; only the coefficient R-height to S-height alters insofar as, during the first days of life, the coefficient resembles that found

in older adults, while it changes later on to that found in children and younger adults."

It is therefore evident, from the literature just mentioned, that electrocardiographic studies have been made from before birth up to the ninth and tenth

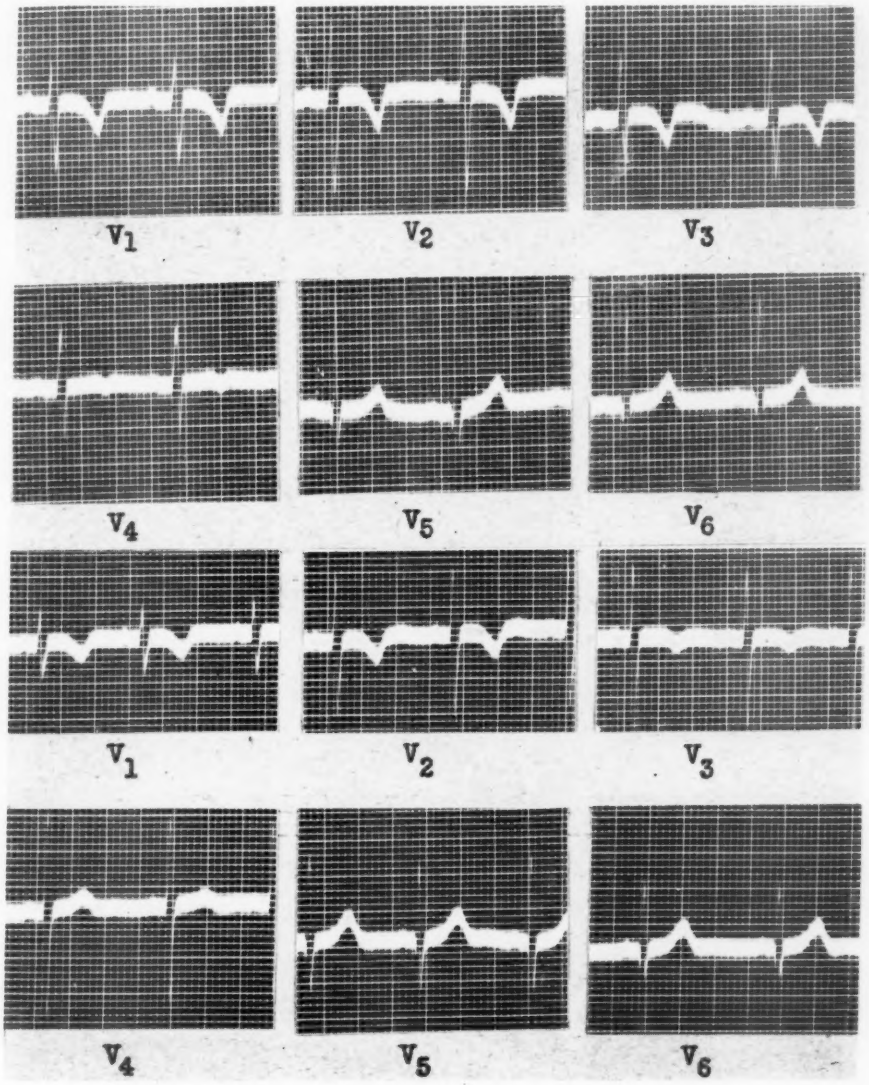

Fig. 5.—*A*, Case 963. A. L. P., aged 10 years, male. Negative and deep T wave in V_1, V_2, V_3, and V_4. *B*, Case 949. V. G., aged 8 years, male. Negative T wave only in V_1, V_2, and V_3. Age alone is not the deciding factor.

decades of life. A gap exists, however. The age-group between 15 to 18 years has been overlooked or ignored by the investigators, or perhaps this group has simply been considered uninteresting, electrocardiographically.

It is a well-known fact that normal children often show inverted T waves in the leads from the right side of the precordium, but just how old the subject must be before such T waves should be regarded as probably abnormal has not been determined. We shall attempt to determine in this study, first, the approx-

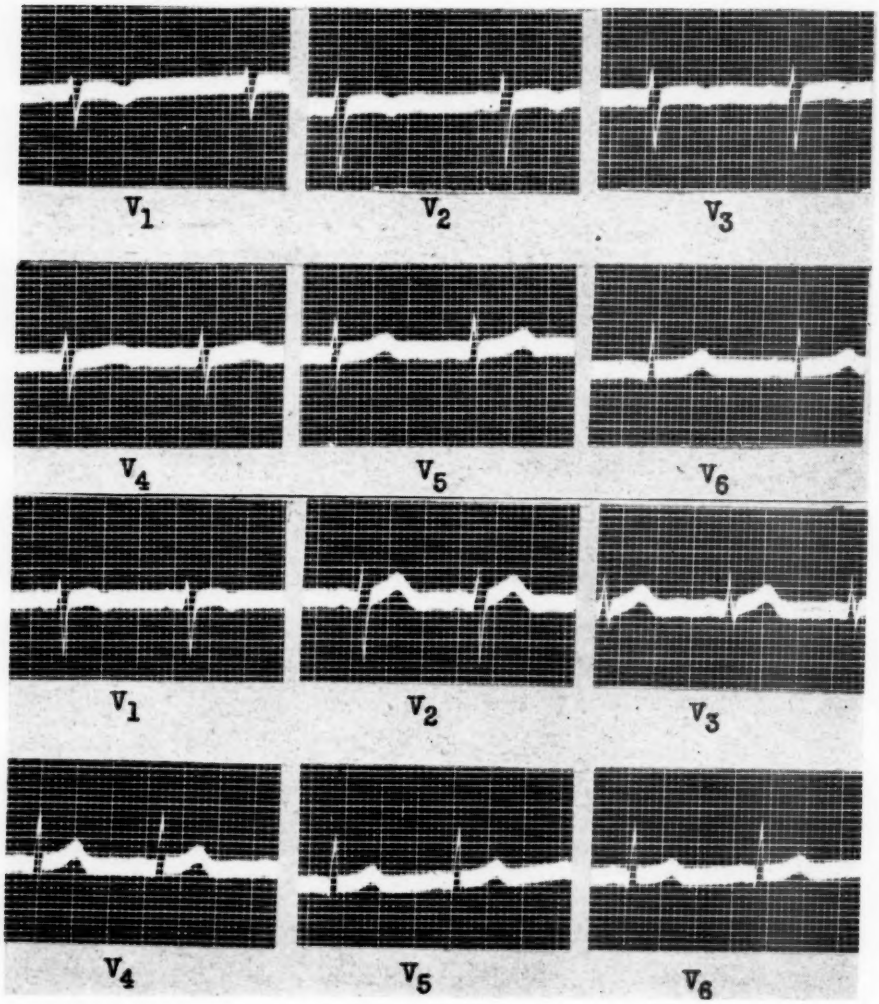

Fig. 6.—*A*, Case 938. G. M. G., aged 18 years, female. Negative T waves in V_1, V_2, and V_3. *B*, Case 933. I. I. L., aged 17 years, female. Negative T wave only in V_1. Although this patient was younger than the one in *A*, the adult pattern of the precordial electrocardiogram is present.

imate age at which a negative T wave may be considered abnormal and, second, whether or not the potential variations in the T wave are influenced by sex.

The T wave represents the main recession of the electrical impulse in the ventricle and is inscribed during ventricular contraction. It is the most unstable part of the electrocardiogram. Many physiologic conditions that will not affect

the QRS complex may alter the appearance of the T wave: heat and cold, digestion, change of position from the supine to the sitting or standing, nervous disturbances, and so forth. Cold applied to the apex will change a positive T wave

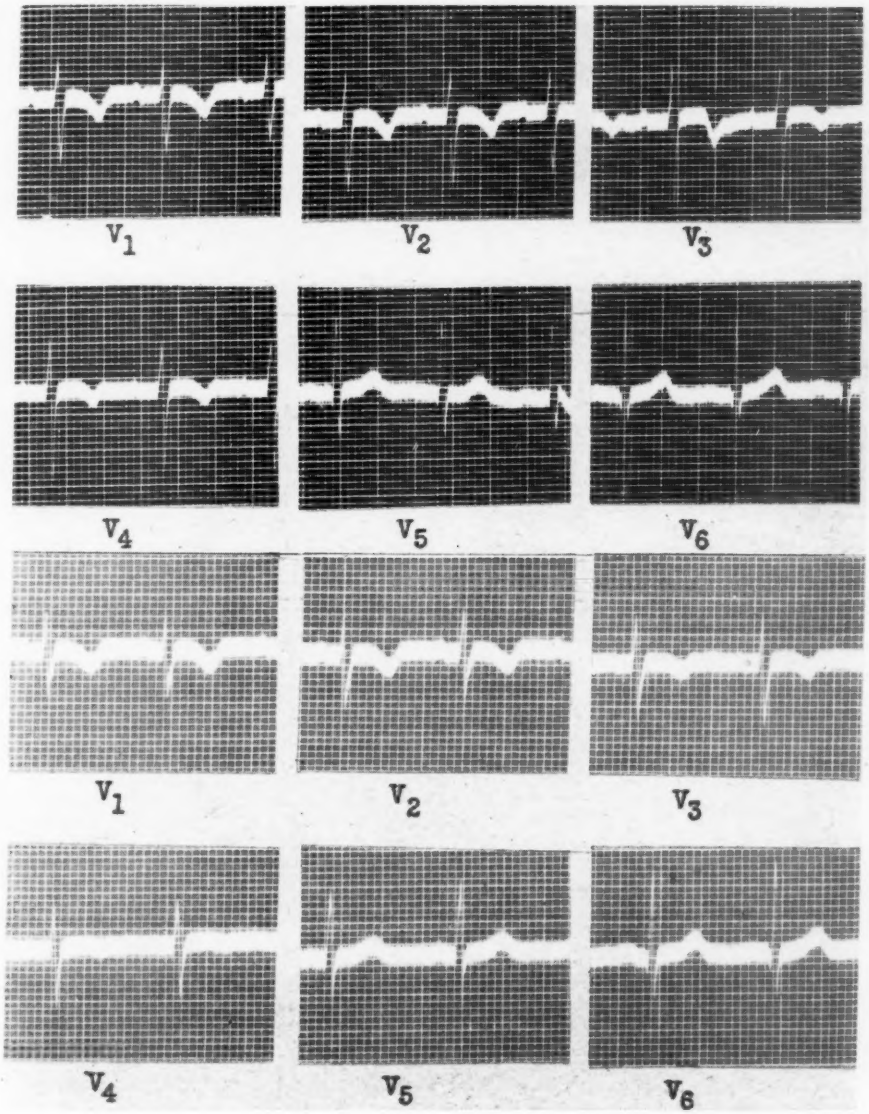

Fig. 7.—*A*, Case 7. R. N., aged 7 years, female. Negative T waves in V_1, V_2, V_3, and V_4. More marked negativity of T in V_4 than in patient in *B*, who is only 5 years of age. *B*, Case 3. M. C. B., aged 5 years, female. Negative T waves in V_1, V_2, V_3, and V_4.

to a negative one, because the cold shows the process of retreat. This has been shown by Wilson and Finch[18] to occur in normal persons as a result of drinking cold water. Ashman and Hull,[19] however, do not favor the idea that the sequence

TABLE I. T-WAVE SHAPE*

AGE AND SEX	NO.	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-46 yr.	50	32 R 10 F 7 D ± 1 D ∓	45 R 1 F 4 D ±	48 R 2 P	44 R 6 P	47 R 3 P	50 R
Female adults 19-45 yr.	31	20 R 8 F 2 D ± 1 D ∓	27 R 2 F 1 D 1 P	28 R 2 F 2 P	31 R	31 R	31 R
Male youngsters 12-18 yr.	20	19 R 1 D	12 R 1 F 5 D 1 P 1 Nt.	12 R 5 D 2 D 1 P 2 Nt.	18 R 2 D	20 R	20 R
Female youngsters 12-18 yr.	20	17 R 2 F 1 D	14 R 2 F 1 D	18 R 1 F 1 Nt.	20 R	20 R	20 R
Male children 5-11 yr.	20	18 R 2 D	9 R 11 D	9 R 10 D 1 Nt.	19 R 1 D	19 R 1 P	19 R 1 P
Female children 5-11 yr.	20	20 R	13 R 7 D	15 R 1 F 4 D	18 R 1 F 1 D	18 R 2 P	19 R 1 P

*R = Rounded; F = flat; D = diphasic; P = pointed; Nt. = notched.

TABLE II. T-WAVE DURATION (IN SECONDS)

AGE AND SEX	NO.	DURATION	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-46 yr.	50	Min. Max. Av.	0.08 0.26 0.16	0.14 0.27 0.21	0.14 0.32 0.23	0.18 0.32 0.23	0.16 0.30 0.22	0.12 0.24 0.21
Female adults 19-45 yr.	31	Min. Max. Av.	0.06 0.20 0.136	0.08 0.24 0.167	0.10 0.28 0.196	0.12 0.28 0.190	0.12 0.24 0.181	0.12 0.20 0.161
Male youngsters 12-18 yr.	20	Min. Max. Av.	0.04 0.20 0.117	0.08 0.28 0.177	0.08 0.28 0.196	0.16 0.28 0.205	0.12 0.28 0.188	0.10 0.20 0.154
Female youngsters 12-18 yr.	20	Min. Max. Av.	0.08 0.18 0.115	0.08 0.20 0.155	0.12 0.24 0.175	0.16 0.24 0.175	0.12 0.24 0.167	0.12 0.20 0.155
Male children 5-15 yr.	20	Min. Max. Av.	0.12 0.18 0.128	0.08 0.18 0.141	0.08 0.24 0.142	0.10 0.24 0.179	0.16 0.24 0.191	0.16 0.20 0.177
Female children 5-15 yr.	20	Min. Max. Av.	0.12 0.18 0.149	0.08 0.16 0.136	0.08 0.26 0.157	0.08 0.24 0.181	0.12 0.24 0.178	0.12 0.20 0.178

of repolarization of the ventricular muscle is due to a difference in temperature; they are inclined to accept the suggestion of Dr. A. C. Young to the effect that the subendocardial muscle layers, being probably subjected to a higher pressure during systole than the subepicardial, may repolarize more slowly, particularly in the left ventricle and left side of the septum.

The ascending limb of the T wave rises slowly and inscribes a slight upward concavity; the descending limb comes down more abruptly. The apex, or peak, is therefore at a slightly greater distance from the base of the ascending limb than from that of the descending limb. In the negative wave, the descending limb descends more slowly with a tendency to inscribe an upward convexity, while the ascending limb rises more abruptly. The apex, or peak here, is farther away from the base of the descending limb than from that of the ascending limb. This apex, or peak, may be sharp and pointed, or more or less blunt. The wave may appear positive, isoelectric, diphasic, or negative.

Table I shows the shape or form of the T wave at the various precordial points: V_1, V_2, V_3, V_4, V_5, and V_6. "R" represents both the positive and negative T waves, when they are blunt or rounded. "F" represents the flat or isoelectric T waves; "D" the diphasic; "Nt." the notched; and "P" represents the pointed T waves of high voltage. In V_1, both the children and the young boys and girls showed rounded T waves while only 64 per cent of the male a per cent of the female adults did. On the other hand, almost all the male and female adults showed the normal concavity of the T wave in V_2, while only 60 per cent of the young boys, 70 per cent of the young girls, 45 per cent of the male and 65 per cent of the female children showed this form of T wave. The number of flat and diphasic T waves, which were more frequently observed at points V_2 and V_3, diminished when we advanced to the left side of the heart so that in V_6, all T waves appeared rounded or blunt in shape, except for one pointed T wave in the group of male and another in the group of female children. Most of the pointed and high T waves were observed in V_3, V_4, and V_5 of the group of male adults. There were more diphasic T waves in V_2 and V_3 of the group of male children than in any other group.

Although the duration of the T wave is probably of no particular importance and is difficult to measure accurately, we are reporting our findings in Table II. The duration of the T wave appears to be always less in V_1 than in V_6 of all groups, and slightly longer in the group of male adults than in all the other groups.

The voltage of the T wave appears in Table III. Each millimeter represents 0.20 millivolt. In order to express our results in millivolts, we would have to multiply the figures by 0.2. The highest T wave was 6.25 mm. in V_4 of the group of male adults; the lowest, -4.25 in V_2 of the group of male children. The wave appeared highest in V_4 and V_5 than at the other points, and higher in the adult males than in the adult females, and in the group of children than in the group of young boys and girls. The children and the adult males, therefore, exhibited the highest T waves in this series. With only one or two exceptions, the negative T wave was lower in V_1 than in V_2. This is not the usual finding in coronary thrombosis.

In Table IV we have arranged the number of positive, negative, diphasic, and flat T waves found in the various groups. In V_1, 18 men (36 per cent) and 16 women (51 per cent), 13 young boys (64 per cent) and 17 young girls

TABLE III. T-WAVE VOLTAGE IN MILLIMETERS (1 MM. = 0.20 MU.)

AGE AND SEX	NO.	VOLTAGE	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-45 yr.	50	Min.	−2.5	0.5	1.25	2.00	1.25	0.50
		Max.	2.5	5.25	6.00	6.25	5.00	4.00
Female adults 19-45 yr.	31	Min.	−1.50	−1.25	−0.25	1.25	1.00	1.00
		Max.	2.25	3.00	3.50	4.00	3.50	2.50
Male youngsters 12-18 yr.	20	Min.	−2.50	−2.50	−0.75	1.00	1.00	1.00
		Max.	1.25	4.50	4.25	4.00	4.50	4.25
Female youngsters 12-18 yr.	20	Min.	−1.25	−0.75	−0.50	0.50	1.00	0.50
		Max.	1.00	3.00	2.25	3.00	2.75	2.50
Male children 5-11 yr.	20	Min.	−3.75	−4.25	−3.00	−1.75	1.50	2.00
		Max.	−0.75	1.75	1.50	3.50	5.00	5.75
Female children 5-11 yr.	20	Min.	−3.00	−2.75	−2.00	−1.50	−1.00	1.25
		Max.	−1.00	1.25	3.00	5.25	5.00	3.50

TABLE IV. T WAVE; NUMBER OF POSITIVE, NEGATIVE, DIPHASIC, AND FLAT T WAVES

AGE AND SEX.	NO.	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-46 yr.	50	18 −(36%) 8 D 10 F 14 +	0− 4 D 1 F 45 +	All +	All +	All +	All +
Female adults 19-45 yr.	31	16 −(51%) 3 D 8 F 4 +	4 − 1 D 2 F 24 +	1 − 2 F 28 +	All +	All +	All +
Male youngsters 12-18 yr.	20	13 −(64%) 1 D 6 +	4 − 5 D 1 F 10 +	1 − 5 D 14 +	0 − 2 D 18 +	All +	All +
Female youngsters 12-18 yr.	20	17 −(85%) 1 D 2 F 0 +	2 − 1 D 2 F 15 +	1 − 1 F 18+	All +	All +	All +
Male children 5-11 yr.	20	18 −(90%) 2 D 0 +	9 − 11 D 0 +	6 − 10 D 4 +	1 − 1 D 18 +	All +	All +
Female children 5-11 yr.	20	20 −(100%)	13 − 7 D 0 +	8 − 4 D 1 F 7 +	3 − 1 D 1 F 15 +	1 − 19 +	All +

(85 per cent), and 18 male (90 per cent) and 20 female (100 per cent) children showed a negative T wave.

In V_2, there was no negative T wave for the group of male adults, but there were four diphasic and one isoelectric T wave. There were four negative T waves (13 per cent) in the group of female adults, with one diphasic and two flat or isoelectric; four (20 per cent) in the group of young boys, with five diphasic and one flat; two negative with one diphasic and two flat in the group of young girls; nine negative T waves (45 per cent) in the male children, with 11 diphasic; and 13 negative T waves (64 per cent), with seven diphasic in the group of female children. The frequency of negative T waves diminished rapidly from V_3 to V_6, and there was not a single instance of negative T waves in V_6.

In the group of male adults, negative T waves were observed only in V_1 (Figs. 1, 2, and 3). The groups of female adults and of the young boys and girls presented negative T waves in V_1, V_2, and V_3. Several women between the ages of 18 and 34 showed negative T waves in V_1 and V_2. The male children presented negative T waves as far to the left as point V_4, one female child reaching point V_5.

In general, it may be stated that negative T waves in the precordial electrocardiogram are more frequent in the female than in the male sex, except at the age level between 12 and 18 years, at which the incidence is similar. This may be explained by the fact that girls between 12 and 18 are more mature physically than boys of the same age.

Table V gives the percentages of all negative, diphasic, and flat T waves found at the various precordial points. The similarity existing beween the groups of young girls and of the women, and the difference between the precordial electrocardiogram of the young boys and of the men, is again evident. Children, male and female, gave similar percentages, but there appears to be a slight tendency to more negative T waves in the girls.

TABLE V. T WAVE; PERCENTAGE OF NEGATIVE, DIPHASIC, AND FLAT T WAVES

AGE AND SEX	NO.	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-46 yr.	50	72	10	0	0	0	0
Female adults 19-45 yr.	31	87	22	9	0	0	0
Male youngsters 12-18 yr.	20	70	50	30	5	0	0
Female youngsters 12-18 yr.	20	95	25	10	0	0	0
Male children 5-11 yr.	20	100	100	80	5	0	0
Female children 5-11 yr.	20	100	100	65	25	5	0

TABLE VI. S-T SEGMENT; NUMBER OF CASES AND NUMBER IN MM. ABOVE OR BELOW THE ISOELECTRIC LINE

AGE AND SEX	NO.	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-46 yr.	50	4 + 1	6 + 1 1 + 1.5	7 + 1 1 + 1.5	7 + 1	1 + 1.5	1 − 1
Female adults 19-45 yr.	31	2 + 1	1 + 1 2 + 0.5	1 + 1 1 − 0.5	1 + 1	0	1 + 1
Male youngsters 12-18 yr.	20	0	1 + 1	1 + 1	1 + 1.25 1 + 0.5	1 + 1 1 + 0.5	1 + 0.5
Female youngsters 12-18 yr.	20	2 + 1 1 + 0.5	1 + 1 2 + 0.5	5 + 0.5	2 + 0.5	1 + 0.5	1 + 0.5
Male children 5-11 yr.	20	0	0	0	0	0	0
Female children 5-11 yr.	20	1 + 0.5	3 + 0.5	2 + 0.5	1 + 1 1 + 0.5	1 + 1 1 + 0.5	0 2 + 0.5

Only one case *below* isoelectric line −1 mm. in V_6 in a male adult.
Only two cases more than 1 mm. above isoelectric line (+1.25 mm.); in male youngster (18 years of age) and one male adult (+1.5 mm.).
S-T segment on line in all male children from 5 to 11 years of age.
Female children of the same age group showed slight deviation.

Table VI reveals that deviation of the S-T segment from the isoelectric line was a relatively rare finding. Only one case, a male adult, showed negative deviation of 1 mm. (at point 6). The boys from 5 to 11 years showed no deviation of the S-T segment. The highest deviation (+1.5 mm.) was observed once in the group of male adults, but the usual deviation was from +0.50 to +1 millimeter.

We are also presenting the precordial electrocardiograms, obtained from two subjects of each of the groups studied, which show the various patterns at different age levels and the pronounced fluctuations in the T waves of different subjects of the same, or approximate, age (Figs. 1 to 7). The legend for each figure is self-explanatory.

SUMMARY AND CONCLUSIONS

We have presented a study of the T wave of the unipolar precordial electrocardiogram in 161 healthy Puerto Ricans, both male and female, between the ages of 5 and 46 years.

The form and voltage of the T wave, as well as the deviation of the S-T segment from the isopotential line, have been determined.

The study suggests that, independent of age levels and sex, a negative T wave in V_1 may be considered normal, and a negative T wave in V_6 should be considered abnormal.

In the male adult of over 19 years of age, a negative T wave in V_2, V_3, V_4, V_5, and V_6 is probably abnormal, especially at the last four points. In the adult

female of the same age, and in the young girls and boys 12 to 18 years of age, a negative T wave in V_4, V_5, and V_6 may be considered abnormal. In children from 5 to 11 years, a negative T wave is probably abnormal only when present in V_6 and perhaps V_5.

Deviations of the S-T segment in the precordial electrocardiogram should be considered normal when such deviation is positive and does not go over 1.5 mm. in the adult or above 1 mm. in children. An S-T segment 1mm. below the isoelectric line was found only once—at point 6, in a male adult.

This study further suggests that, in addition to age and sex and such physiologic factors as cold, change of position, digestion, and nervous disturbances, there are other, yet undetermined, intrinsic factors that may influence the T wave of the precordial electrocardiogram in normal persons.

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DISADVANTAGES OF THIOURACIL TREATMENT OF ANGINA PECTORIS

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DESPITE the numerous reports[1-6] concerning the beneficial results to be obtained by total thyroidectomy for angina pectoris, this procedure has gained small popularity. With the advent of thiouracil,[7] a drug capable of lowering oxygen consumption, even when the thyroid gland is normal,[8,9] a means became available to reinvestigate this problem.

In 1944 we began to administer thiouracil to a limited number of cardiac patients with proved coronary artery disease and severe angina pectoris, keeping close watch on the level of oxygen consumption, the degree of anginal pain, and the exercise tolerance. Since then a publication[10] has appeared which reports startlingly good results from this type of therapy. Our own results are not encouraging for the reasons to be outlined below, and it appears desirable to record them.

METHODS

Only patients who had been observed both on the wards and in cardiac clinic for several years were studied. This was desirable so that the subjective symptoms of angina pectoris might be better evaluated. Every clinician is acquainted with the variability of anginal pain, changing as it does with the season and the frame of mind of the patient. We desired to make sure of the consistency of the anginal pain of our patients by the best means available: a close personal acquaintance with the patient over an extended period of time.

All of the eight male patients included in this report had severe coronary artery disease. Electrocardiographic and clinical evidence indicated that six of them had had coronary occlusions with myocardial infarctions one to two years previous to the time of our study. The remaining two patients (Table I) gave no history of myocardial infarction. One patient, F. P., had a normal electrocardiogram at rest. However, after exercise the tracing showed marked depression of the S-T segment in Lead II, indicating marked myocardial ischemia. Moreover, both the systolic and diastolic blood pressure always fell after exercise. The second patient, L. P., was the only one of the group with a valvular lesion. He had severe rheumatic heart disease with marked aortic insufficiency. The

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TABLE I. RESULTS OF THIOURACIL THERAPY IN EIGHT NONHYPERTENSIVE CARDIAC PATIENTS

PATIENT	AGE	DIAGNOSIS	DAILY DOSE OF THIOURACIL (GM.)	LENGTH OF TREATMENT	EXERCISE TOLERANCE (NO. OF FOOT-POUNDS)		CONTROL (B. M. R.)	MAXIMUM DEPRESSION OF B. M. R.	PRECORDIAL PAIN	RESULTS	COMMENT
					BEFORE TREATMENT	MAX. AFTER TREATMENT					
F. P.	55	Arteriosclerotic heart disease	0.6	59 days	5,100	7,395	+9	−11	No change	Poor	Toxic rash from thiouracil
I. F.	64	Arteriosclerotic heart disease	0.6	53 days	6,987	10,332	−7	+22	No change	Poor	Impossible to lower B. M. R. with dose used
M. G.	58	Arteriosclerotic heart disease	0.6	21 days	7,434	13,275	+45	+41	No change	Poor	Allergic to thiouracil, developed rash on two occasions
L. P.	34	Rheumatic heart disease; aortic insufficiency	0.6	26 days	7,380	30,012	+10	−10	Improvement, then severe recurrence	Poor	Developed severe dyspnea under treatment
F. T.	59	Arteriosclerotic heart disease	0.6	1 yr., 2 mo.	4,260	22,440	+55	−35	Marked improvement	Good	May be a case of masked hyperthyroidism
J. K.	51	Arteriosclerotic heart disease	0.6 to 0.8	1 yr., 1 mo.	14,520	33,278	−10	−20	Improvement, then recurrence	Poor	Developed symptoms of coronary occlusion on full doses of thiouracil
L. F.	54	Arteriosclerotic heart disease	0.6	1 yr., ½ mo.	4,437	14,445	+25	−15	Marked improvement	Excellent	Able to resume work for a short period
N. S.	54	Arteriosclerotic heart disease	0.6 to 1.2	1 yr., ½ mo.	3,949	13,266	0	−22	Limited improvement	Fair	Status anginosis; no real relief except at myxedema level

systolic blood pressure was 190 on the average; the diastolic pressure could not be determined since the sounds were still audible at zero. An electrocardiogram showed right bundle branch block. This, with the low diastolic pressure, may be taken as good evidence of myocardial ischemia. None of the patients were hypertensive.

Anginal pain was arbitrarily determined by assigning four degrees of severity of pain for each patient. Naturally, a 4 plus degree of pain for a patient with mild angina was not comparable to a 4 plus degree of pain in the patient with most severe angina. In grading the degree of pain, due consideration was given to the frequency of use of nitroglycerine and to various psychic influences.

An exercise test was done at suitable intervals, usually in the morning, two hours after a light breakfast. A single step nine inches high was used. The patient was always exercised at the rate of 20 to 25 steps per minute. Environmental temperature was kept at 70 to 74° F. Exercise was stopped only at the point of severe anginal pain. We found the exercise test particularly valuable because it enabled us to select patients from the viewpoint of angina rather than dyspnea as a limiting point to their exercise. The results were calculated in foot-pounds to obviate the factor of weight. Obviously a patient weighing 200 pounds doing 20 steps has done more work than a patient weighing 150 pounds doing the same number of steps. Also, with a lowering of the basal metabolic rate, the patients gain weight, and calculation of the results in foot-pounds of work done eliminates an obvious error from this factor.

Blood pressure and pulse rates at rest, immediately after exercise, and at intervals of two, four, and eight minutes after exercise were also taken. Since therapy had little effect upon these figures, they will not be reported.

Thiouracil* was generally administered in daily doses of 0.6 Gm. divided into three 0.2 Gm. portions. As much as 1.2 Gm. in divided daily doses was given to one patient (N. S.), but only while he was hospitalized. The patients were warned to watch for throat infections, fever, or rashes. They were seen weekly to prevent the signs and symptoms of agranulocytosis from escaping notice. None of them had palpable thyroid glands nor did any have the symptoms of hyperthyroidism. Patient F. T. (Table I) had an initial basal metabolic rate of +55 and may have had masked hyperthyroidism.

Placebo tablets resembling in every way the thiouracil tablets were used on two occasions to test the result of cessation of therapy without the patients' knowledge. These contained only small amounts of urea and magnesium sulfate to simulate the taste of thiouracil.

RESULTS

One of the first features to strike our attention was the refractory nature of the normal adult thryroid gland to thiouracil. This was particularly true when the control basal metabolic rate was near the zero level. In Table I it may be seen that patient F. P., after two months of 0.6 Gm. of thiouracil daily,

*Both the thiouracil and the placebo tablets used in this study were supplied through the generosity of Dr. Stanton B. Hardy of the Lederle Laboratories, Inc., Pearl River, N. Y.

had a drop of only from +9 to −11. Similarly, patient I. F. actually had a rise in the basal metabolic rate of from −7 to +22 on the same dosage. In his case considerable dyspnea was present during the final basal metabolic rate determination. This, however, we believe to be the result of a tendency of thiouracil to cause water retention;[8] for this reason the result is valid and is properly included. In the case of M. G., therapy had to be stopped after three weeks because of a marked allergy to thiouracil. He developed a severe maculopapular rash which disappeared in two days. On restarting thiouracil the rash reappeared and therapy had to be terminated. Patient F. P. also developed a much more severe maculopapular rash with scaling, and therapy had to be stopped. It is interesting that in this latter case the rash occurred after thiouracil had been given for two months. Patient L. P. had a fall of the basal metabolic rate of from +10 to −10 on 0.6 Gm. of thiouracil daily for three and one-half weeks. In his case therapy had to be terminated because he acquired a severe constricting sensation in the chest and marked dyspnea, both exertional and nocturnal. In his case also we feel that the thiouracil caused water retention and incipient pulmonary edema, particularly in view of the severe aortic insufficiency.

In these four patients there was no real improvement in the degree of anginal pain. In the first three patients (Table I) exercise tolerance did not improve beyond what could be expected from training. The fourth patient, L. P., had an increase in exercise tolerance of from 7,380 foot-pounds to 30,012 foot-pounds. However, at the end of three weeks of therapy, he could not exercise at all because of dyspnea, so that no real gain was made.

The next four patients were treated for periods over one year and their cases will be described in detail.

CASE F. T. (Table I and Fig. 1).—Treatment was started on this patient in the middle of October, 1944. There was a marked fall in basal metabolic rate of from +55 to −22 after 0.6 Gm. of thiouracil daily for nine weeks. He did not suffer from Graves' disease so far as could be determined clinically. However, the elevated metabolism and especially the sensitivity to thiouracil strongly suggested that he had masked hyperthyroidism. The exercise tolerance quadrupled in the same period, and there was a marked diminution in precordial pain. Before therapy he had been using nitroglycerine daily; after therapy was started, it was required only occasionally. Toward the end of December he was put on placebo tablets for eight weeks. The metabolism then rose to −3. The exercise tolerance continued to improve, then fell sharply at the end of this period; that is, toward the last week of February. The precordial pain remained improved despite the rise in metabolism. He was again started on 0.6 Gm. of thiouracil daily to study the effects of a further lowering of metabolism. This time the thiouracil was continued without interruption for four months, until the end of June. The metabolic rate fell much more slowly this time, starting from a level of −7 and falling to −35 at the end of the period. He acquired definite symptoms of myxedema with a gain of 20 pounds in weight, lethargy, puffy face, and hoarse voice. The exercise tolerance improved at first during the months of March and April but fell gradually during May and June to pretherapy levels. The precordial pain disappeared completely from the end of March through July. In the exercise tolerance test, it is noteworthy that the limiting factor to exercise changed from precordial pain to dyspnea. Another interesting development was the onset of severe intermittent claudication during the period of the greatest depression of metabolism. Naturally, during this period the limiting factor to exercise was calf pain. This is explained by the marked diminution of peripheral blood flow which

is known to occur in myxedema.[11] During August and September thiouracil was not given. The metabolism promptly rose to zero in six weeks' time. The precordial pain returned. The exercise tolerance, however, did not improve appreciably.

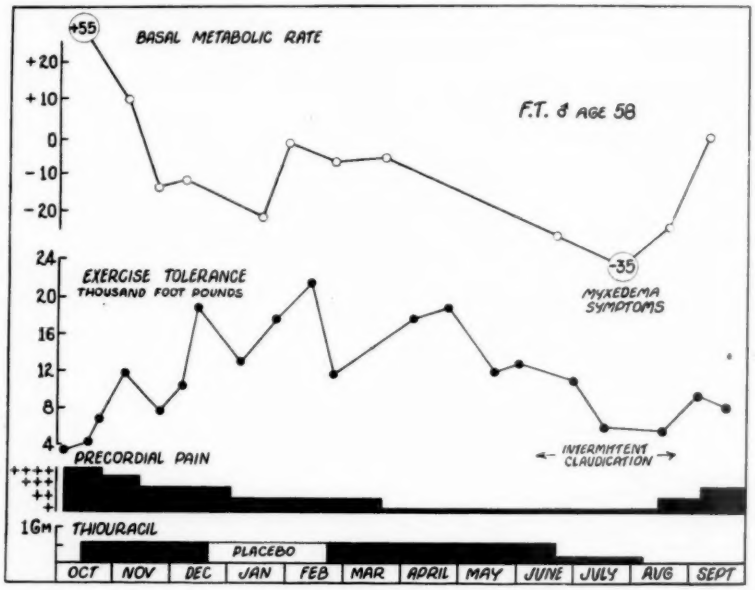

Fig. 1.—Effects of treatment in Patient F. T.

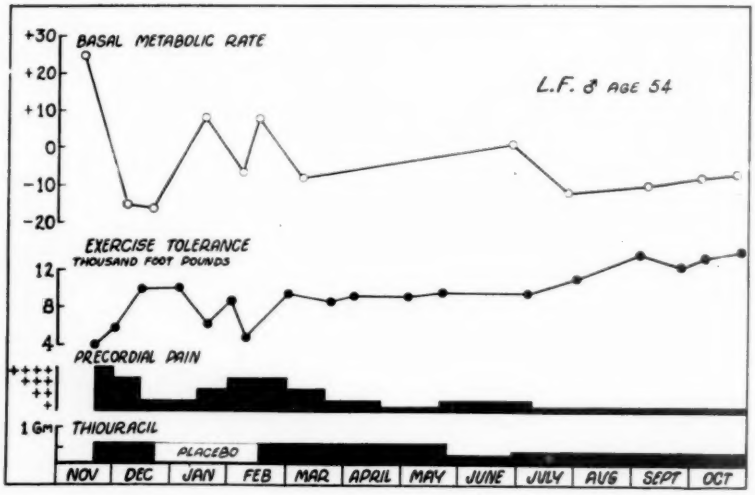

Fig. 2.—Effects of treatment in Patient L. F.

In summary, it may be said that the patient felt best and could do most when the basal metabolic rate was maintained between —10 and —20. Upon

cessation of thiouracil, his symptoms returned with the rising metabolism so that no real gain was made.

CASE L. F. (Table I and Fig. 2).—This patient had a control basal metabolic rate of +25 in November. With only four weeks' therapy with 0.6 Gm. of thiouracil daily, the basal metabolic rate fell to −15 in December. In this period, precordial pain diminished markedly and the exercise tolerance nearly tripled. When placed on placebo tablets, the metabolism rose to +8, fell to −6, and finally rose again to +8. At this time the exercise tolerance showed a closed inverse relationship to the level of metabolism. This was the only instance in the series in which it was possible to demonstrate clearly that when the level of metabolism rises, the ability to exercise falls, and vice versa. With the rise in metabolism the precordial pain returned. He was then put back on 0.6 Gm. of thiouracil daily in February. This was continued until May, when it was cut to 0.3 Gm. daily for one month, then raised to 0.4 Gm. daily until October. On these doses the metabolic rate was maintained at about −10. Precordial pain disappeared completely and the exercise tolerance improved steadily. The patient expressed great satisfaction and was able to return to light work for the first time in two years.

It must be pointed out in this case, however, that the thiouracil must be continued and the patient must be carefully watched to maintain the good results.

CASE N. S. (Table I and Fig. 3).—This was our patient with the most severe angina. He could only walk about fifty feet before he was seized with agonizing precordial pain. The control basal metabolic rate was zero. Starting in November, he was put on 0.8 Gm. of thiouracil daily for two weeks, then on 0.6 Gm. daily for two more weeks. The thiouracil then had to be stopped because of a severe upper respiratory infection. On this course of therapy the metabolism fell

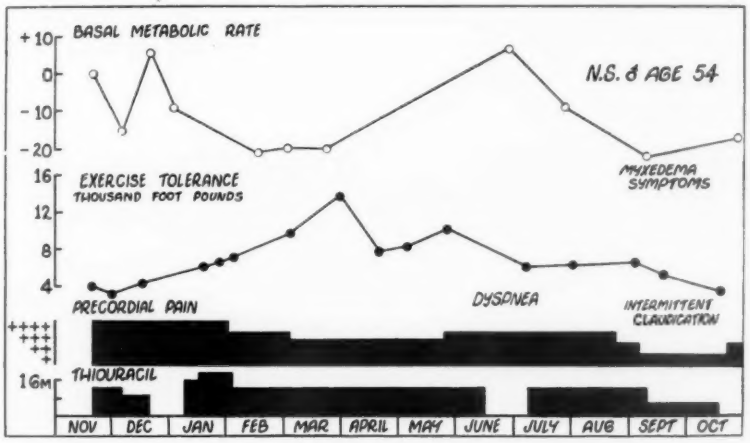

Fig. 3.—Effects of treatment in Patient N. S.

to −16. There was no change in precordial pain and exercise tolerance. It was decided to hospitalize him in January to give him an adequate course of thiouracil under close observation. He was given up to 1.2 Gm. of thiouracil daily in four doses for three weeks. This was then cut to 0.8 Gm. daily and maintained over a period of four and one-half months. At this time, in June, the drug had to be terminated because of the onset of severe nocturnal and exertional dyspnea. On this strenous therapy the precordial pain diminished but little, although the metabolic rate attained a low of −20. The exercise tolerance improved up until April, when it had more

than tripled. After this period, ability to do exercise diminished gradually to control levels. In July the thiouracil was again started at a dosage level of 0.8 Gm. daily. In this instance the metabolic rate fell from +7 to −22, at which time (September) he had all the clinical signs of myxedema. In the entire one-year period, it was only at this time that he experienced any appreciable relief in the precordial pain. Ability to do exercise, however, was markedly curtailed because of the onset of severe intermittent claudication.

In summary, this patient with severe angina pectoris proved to be markedly refractory to thiouracil. A total dose of 209 Gm. of thiouracil over a period of 250 days was required to depress the basal metabolic rate to myxedema levels. Noteworthy is the fact that the control metabolic rate was zero. This brings out the point that the lower the metabolic rate is to begin with, the more difficult it is to depress it with thiouracil. No real gains were made either in improving the degree of precordial pain or in increasing exercise tolerance.

CASE J. K. (Table I and Fig. 4).—This patient had the least anginal pain of the group. He could walk from five to seven city blocks without pain. The control basal metabolic rate was the lowest of the group, −10. He also proved to be refractory to thiouracil. Daily dosage of from 0.6 to 0.8 Gm. only lowered the metabolic rate to −17 over a three-month period. The exercise tolerance more than doubled during this period. On the whole, the precordial pain dimin-

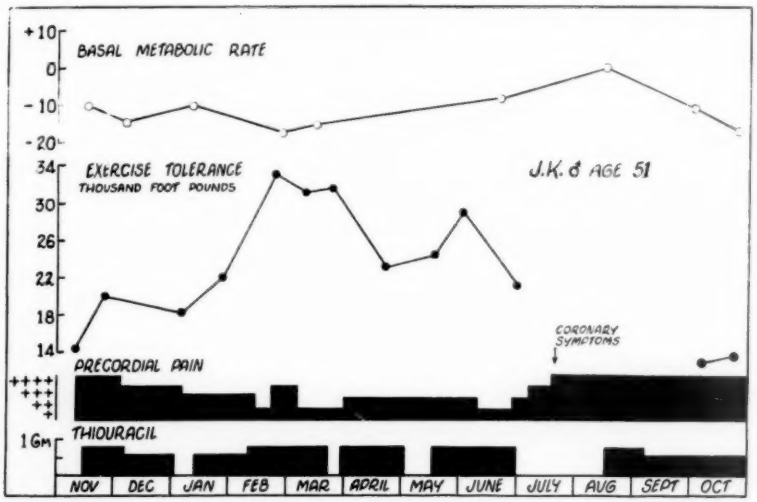

Fig. 4.—Effects of treatment in Patient J. K.

ished considerably, although he still experienced occasional severe attacks. Thiouracil was continued at 0.8 Gm. daily for four more months, until June, with two brief, free periods because of upper respiratory infections. The metabolic rate was not depressed but rose to −10 at the end of the period. For no apparent reason the exercise tolerance also diminished. In July he began to experience severe attacks of precordial pain. At the end of this month the pain became substernal in type and he was hospitalized for a period of bed rest and study. Three serial electrocardiograms did not reveal changes indicative of coronary occlusion, but the sedimentation rate was elevated and he had temperature rise to 101.4° F. which could not be explained. It

was therefore considered wise to treat him for myocardial infarction even in the absence of absolute proof. The precordial pain remained severe for the next four months in spite of the fact that readministration of thiouracil depressed the metabolic rate to −16. When he was again exercised in October, he had returned to control levels.

In summary, this patient who had a low metabolic rate to begin with and relatively mild anginal pain may have been actually harmed by the thiouracil therapy. During the course of therapy he experienced symptoms of coronary occlusion. At the end of a year the anginal pain was worse and the exercise tolerance less than when therapy was started.

DISCUSSION

One point clearly brought out by this study is that depression of the basal metabolic rate diminishes precordial pain. This is most true in patients who have an initially elevated metabolism. Usually to make the precordial pain disappear completely, myxedema levels have to be attained. Thus the effects of total thyroidectomy on angina pectoris are reproducible by thiouracil therapy.[1-6,12]

Does this mean that the coronary circulation is relatively enhanced in the states of diminished thyroid activity? The evidence is greatly against this viewpoint. In myxedema the cardiac output is diminished,[13] blood volume is reduced,[14] and the peripheral blood flow is slowed.[11] The individual's personality changes. He has less drive and less energy. Glandular activity and secretion is lessened. Intestinal absorption is slowed. Thus the beneficial results on coronary circulation could be explained purely on a mechanical basis: less demands are made upon a heart with diminished myocardial reserve. In other words, the individual is forced to live within the limits of his myocardium's ability to do work.

The attractive theory that diminished thyroid activity lessens the sensitivity of the heart to epinephrine has been enlarged upon.[9,10] There is evidence against this theory,[12-15] but, if proved true, it would be an added reason for diminishing thyroid activity in patients with heart disease.

There are, however, many practical disadvantages to both total thyroidectomy and thiouracil therapy. The difficulties of control of the basal metabolism by thyroidectomy have been pointed out.[5] Thiouracil has proved to be rather toxic and no substitutes have been found for it.[16] Moreover, it has to be given for long periods of time and in large doses in order to depress the metabolism of an individual whose metabolism is low initially. As soon as the drug is stopped, the metabolism rises again so that no real gain is made. The greatest difficulty is a tendency for water retention as metabolism is lowered. In certain cardiacs this results in pulmonary edema with nocturnal and exertional dyspnea.* Thus

*We were able to demonstrate this point clinically to our complete satisfaction. A patient with severe hypertensive heart disease and anasarca had been observed on the ward for at least six months. He was kept edema free only by injection of mercurials every third day and strict limitation of salt and fluid intake. Without changing his regimen in any way, he was given 0.6 Gm. of thiouracil daily. After six days he became markedly edematous and had an attack of severe pulmonary edema. The thiouracil was stopped and he promptly recovered. This experiment was repeated on two subsequent occasions with similar results. Thus the tendency of thiouracil therapy to cause water retention was amply demonstrated in this patient. The basal metabolism studies were unsatisfactory because the dyspnea obscured the results.

one defeats his purpose in these instances because obviously the patient is in more trouble with dyspnea than with angina.

It is well known that the amount of cholesterol in the blood rises with a lowering of the metabolic rate. Naturally this predisposes to atherosclerosis. Indeed, one of our patients developed symptoms strongly suggestive of coronary occlusion while on thiouracil therapy; in a former study,[10] one of ten patients did have coronary occlusion. Therefore, there is a real possibility of actually harming a cardiac patient by lowering the metabolic rate even though the pain may be relieved.

Aside from these considerations, is the patient able to do more work after therapy? We found, as others have,[1-6] that the optimum effect in regard to exercise tolerance and well-being in general is obtained at a basal metabolic level ranging from −10 to −20. Above this level the patients have too much anginal pain; below, they are too dull mentally and are apt to have intermittent claudication, as occurred in two of our patients. Even at the optimum level their ability to do work is not great and is sharply limited by a low myocardial reserve. The limiting factor to exercise simply changes from anginal pain to dyspnea or to a general tired feeling. Only one of our patients was able to resume light work. Certainly if a patient has anginal pain when his basal metabolism normally is −10 it would be foolhardy to attempt to improve his condition by further lowering his metabolism.

SUMMARY AND CONCLUSIONS

Thiouracil was administered to eight nonhypertensive cardiac patients with various degrees of anginal pain. All of them had normally functioning thyroid glands, except one who may have had masked hyperthyroidism. Six of these patients had previous coronary occlusion. The seventh had definite electrocardiographic changes indicative of coronary disease after exercise, and the eighth had rheumatic heart disease with severe aortic insufficiency and bundle branch block.

The relationship between the level of metabolic rate, the degree of precordial pain, and exercise tolerance was followed in each patient. In four of the patients, therapy was stopped after periods ranging from three weeks to two months for the following reasons; toxic skin rashes in two instances, onset of severe exertional and nocturnal dyspnea, and failure to lower the basal metabolic rate with the dosage used. No real benefit on either precordial pain or exercise tolerance was experienced by any of these four patients.

The four remaining patients were treated and followed for over a year. In two of them it was possible to attain myxedema levels. In general, precordial pain was beneficially affected, at least for a period of time, in each of these patients; at certain times exercise tolerance was doubled and even quadrupled. However, all of them except one lost his increased ability to do work at the end of the one-year period. One patient had symptoms resembling coronary occlusion during the course of therapy.

The disadvantages of thiouracil as a drug for use in patients with normally functioning thyroid glands may be listed as follows: toxicity of the drug, necessity for close supervision of the patient over long periods of time, inability to lower metabolism when the basal metabolism is low to start with, tendency toward water retention, particularly deleterious in cardiac patients, and necessity for continual therapy in order to maintain results.

Thiouracil therapy for angina pectoris is therefore not recommended as a routine procedure. It is indicated in angina pectoris, when the basal metabolic rate is elevated, and can be used as a therapeutic test by those who wish to select patients with angina pectoris for thyroidectomy.

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CARDIOVASCULAR DEFECTS IN SELECTIVE SERVICE REGISTRANTS

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CARDIOVASCULAR defects have consistently ranked among the five leading causes for rejection of men liable for military service who were physically examined through the Selective Service System since 1940. Some cardiovascular defect was considered the most important cause for rejection of one in every fourteen men disqualified for military service at the end of 1944. In addition, approximately the same ratio of the World War II veterans who were receiving disability pension awards in the fall of 1944 had cardiovascular defects as their major disability.

The widespread prevalence of heart defects among men 18 through 44 years of age is not surprising, since heart disease is the leading cause of death among men between the ages of 25 and 44 and third in importance as a cause of death among those 15 through 24 years of age. These defects were found in 83 of every thousand registrants examined by Selective Service local board physicians during 1940 and 1941, the peacetime period of Selective Service operation. Valvular heart disease (rheumatic and syphilitic) and arterial hypertension were the most frequent diagnoses recorded, as well as the leading causes for rejection of Selective Service registrants during both peacetime and wartime.

The Armed Forces' standards for acceptance of registrants with cardiovascular defects have undergone only slight changes since 1940.* Differences

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From the Medical Division and the Division of Research and Statistics, National Headquarters, Selective Service System.

This report is based on sample studies of the results of examinations recorded on DSS Form 200, Reports of Physical Examination, for Selective Service registrants physically examined at local boards during 1940-1941, and DSS Form 221, Reports of Physical Examination and Induction, for registrants examined at local boards and induction stations during 1942-1944. Coverage of the sample studies varied from 10 to 25 per cent of the examinations. Additional data on cardiovascular defects among Selective Service registrants are contained in the following bulletins published by National Headquarters of the Selective Service System: Folk, O. H., McGill, K. H., and Rowntree, L. G.: Medical Statistics Bulletin No. 1, Analysis of Reports of Physical Examination, Nov. 10, 1941; Edwards, T. I., McGill, K. H., and Rowntree, L. G.: Medical Statistics Bulletin No. 2, Causes of Rejection and Incidence of Defects, An Analysis of Reports of Physical Examination From 21 Selected States, Aug. 1, 1943; Greve, C. H., McGill, K. H., and Rowntree, L. G.: Medical Statistics Bulletin No. 3, Physical Examination of Selective Service Registrants During Wartime, Nov. 1, 1944.

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*The cardiovascular standards for acceptability of Selective Service registrants are contained in War Department Mobilization Regulations 1-9: Standards of Physical Examination During Mobilization. In general, the only cardiovascular defects which were acceptable were (a) a pulse rate of 100 or over if not persistent and not due to paroxysmal tachycardia; (b) a pulse rate of 50 or under which is proved the natural rate, or a temporary rate, or due to drugs; (c) sinus arrhythmia; and (d) temporary elevation of blood pressure due to excitement. A pulse rate of 50 beats per minute became unacceptable in April, 1944, but the change had little effect on the rate of rejection of registrants. No registrants with cardiovascular defects were acceptable for limited service.

in examining procedures, however, as well as in application of the cardiovascular criteria, produced differences both in the rates of rejection for cardiovascular defects and in the diagnoses of certain specific defects in the group. During 1940 and 1941, all the registrants receiving physical examination were examined by local board physicians, who were usually general practitioners. Most of the rejections during this time occurred at the local board level. The physical standards were high, and most of the rejections were made on diagnoses of physical rather than mental defects. The situation was reversed beginning in early 1942, when physical standards were lower, particularly in reference to dental and visual defects, and local board physicians rejected only those registrants with the more serious defects which were manifestly disqualifying. After that, most of the rejections were made by specialists at the induction stations, where psychiatric examinations, blood pressure readings, and other special tests were given only as a part of the routine examination at the Armed Forces' induction stations.

The rates of rejection for cardiovascular defects presented in this discussion and their relative importance as causes for rejection are based on their occurrence as the most serious defects for which the registrants were rejected. The tables showing the prevalence of these defects among all registrants include, in addition to the principal causes for rejection, disqualifying heart defects which were secondary causes for rejection and also the less serious heart defects such as transient hypertension, arrhythmias, and functional murmurs.

NUMBER CURRENTLY REJECTED

Among the nearly five million registrants who were classified as unfit for any form of military service as of January 1, 1945, an estimated 300,100, or 6.7 per cent, had been rejected because the principal defect was cardiovascular (Table I). This figure includes not only the registrants in Class 4-F on that date, but also those who had been rejected for cardiovascular defects and later reclassified in occupationally deferred classes because they were in essential industry or agriculture. It does not include, however, registrants who had been rejected for cardiovascular defects who were re-examined at a later date and inducted or were again rejected for a primary cause which was not cardiovascular.

TABLE I. ESTIMATED NUMBER OF REGISTRANTS AGED 18 TO 37 YEARS IN REJECTED CLASSES BECAUSE OF CARDIOVASCULAR DEFECTS,* JAN. 1, 1945

RACE	TOTAL IN REJECTED CLASSES	REJECTED FOR CARDIOVASCULAR DEFECTS	
		NUMBER	PERCENTAGE OF TOTAL
All races	4,493,000	300,100	6.7
White†	3,621,000	250,900	6.9
Negro	872,000	49,200	5.6

*Includes registrants in Class 4-F and also those transferred from Class 4-F to the occupationally deferred classes, 2-A (F), 2-B (F), and 2-C (F).

†Includes all races other than Negro.

Registrants who were rejected for cardiovascular defects were the fourth group in order of importance, exceeded only by those rejected for mental disease, mental deficiency, and musculoskeletal defects. Relatively more white than Negro registrants who were rejected had cardiovascular defects as the principal cause for their rejection.

The specific diagnosis in more than four of every ten rejections for cardiovascular defects was valvular heart disease, most of which was rheumatic in origin. Arterial hypertension was recorded as the diagnosis in three of every ten cardiovascular rejections.

REJECTION RATES FOR CARDIOVASCULAR DEFECTS

The number of registrants rejected for cardiovascular defects decreased from 44 of every thousand registrants physically examined in 1940 and 1941 to 35 per thousand examined in 1944 (Table II). Much of the decrease was the result of the changes in examining procedure discussed previously, which gave an increased value to and a resulting increase in the rate of rejection for neuropsychiatric defects. Other factors, which also effected a decrease in rejection rates for all defects combined, were: (1) changes in the age composition of the group which was subject to induction into the Armed Forces; (2) lower standards for acceptance, particularly those pertaining to dental and visual defects and educational deficiency, during wartime; (3) a Presidential order at the end of 1942, prohibiting the direct enlistment of men 18 through 37 years of age at Armed Forces' recruiting stations.* This cessation of voluntary enlistments made available for examination through Selective Service a large number of physically fit registrants who would not otherwise have been represented in Selective Service data.

TABLE II. ESTIMATED REJECTION RATES FOR CARDIOVASCULAR DEFECTS, BY RACE, 1940-1944*

YEAR	ALL RACES	WHITE†	NEGRO
1940-1941	43.6	44.1	39.6
1942	35.0	33.8	42.5
1943	29.1	27.3	38.6
1944	34.7	33.4	43.5

*Rate per 1,000 examined.
†Includes all races other than Negro.

Among white registrants, the rates of rejection for cardiovascular defects decreased from 44 of each thousand examined in 1940 and 1941 to 33 per thousand examined in 1944. On the other hand, Negro cardiovascular rejection rates tended to increase during wartime, when the majority were examined at induction

*During 1940-1941, the ages of men designated as liable for military service were 21 through 35 years; during 1942, they were 20 through 44 years; and in the two succeeding years, registrants 18 through 37 years were liable, with increasing emphasis during 1944 on the induction of men under 26 years of age.

stations where routine blood pressure readings were made. This is borne out by the fact that hypertension was responsible for almost one-half the Negro cardiovascular rejections during the first two wartime years.

SPECIFIC DIAGNOSTIC GROUPS OF CARDIOVASCULAR DEFECTS

Although cardiovascular defects were recorded on the physical examination reports of 83 registrants in every thousand examined by local board physicians during 1940 and 1941 (Table III), they were the most important causes for rejection of only 44 per thousand examined. They were noted either as secondary causes for rejection or as minor or functional defects in the remaining 39 cases per thousand. The more serious defects, such as valvular heart disease, were almost invariably cause for rejection, so their rates of prevalence and rejection were approximately equal. On the other hand, arrhythmias, functional murmurs, and tachycardia were more important among the total number of physically examined registrants than among those rejected.

TABLE III. PREVALENCE OF CARDIOVASCULAR DEFECTS AND PERCENTAGE DISTRIBUTION OF REJECTIONS FOR THESE DEFECTS AMONG REGISTRANTS PHYSICALLY EXAMINED AT LOCAL BOARDS, 1940-1941*

MAJOR SUBGROUP	PREVALENCE PER 1,000 EXAMINED			PERCENTAGE DISTRIBUTION OF REJECTIONS		
	ALL RACES	WHITE†	NEGRO	ALL RACES	WHITE†	NEGRO
Total cardiovascular	83.1	84.6	71.8	100.0	100.0	100.0
Rheumatic and valvular	28.4	28.5	26.0	44.1	44.6	40.0
Hypertension, arterial	16.6	16.3	19.1	31.6	30.6	40.0
Tachycardia, persistent	6.7	7.2	3.0	8.4	8.8	5.0
Cardiac hypertrophy	2.8	2.8	3.0	2.5	2.5	2.5
Cardiac arrhythmia	5.5	5.8	3.8	1.8	1.8	1.3
Cardiovascular diseases, other‡	4.1	4.3	2.8	6.5	6.7	5.0
Functional murmurs	5.0	5.2	4.3	0.6	0.6	0.5
Other cardiovascular defects§	14.0	14.5	9.8	4.5	4.4	5.7

*Corresponding data for induction stations are not available for the period 1940-1941.

†Includes all races other than Negro.

‡Includes diseases of the heart and vascular system in which the physician recorded a diagnosis other than rheumatic heart disease, valvular heart disease, hypertension, hypertrophy, tachycardia, or arrhythmia.

§Includes entries describing signs, symptoms, or diseases of the heart and circulatory system not elsewhere classifiable, such as: bradycardia, arteriosclerosis, arterial hypotension, and hypertension or tachycardia described as nervous or functional in type.

Valvular heart disease was the most frequently recorded cardiovascular defect. It occurred in 28 of every thousand registrants examined during peacetime. Rheumatic fever was specified as the etiology in only 4 per thousand of

these cases.* The valvular heart disease category also included diagnoses of defects of specified valves and systolic murmurs unspecified as to type. These unspecified systolic murmurs accounted for almost 10 per cent of all the cardiovascular defects recorded. In 79 per cent of the cases where the valve was specified (excluding definite rheumatic heart disease) the mitral valve was affected, in 14 per cent the aortic valve was affected, and in 4 per cent both the aortic and the mitral valves were affected. Endocarditis, which is frequently preceded or accompanied by rheumatic involvement, was recorded for less than one registrant in every thousand examined.

The prevalence rate of such cardiovascular defects as hypertension, tachycardia, cardiac arrhythmias, murmurs, and hypertrophy is slightly understated, for the reason that they were often recorded as observations on which a specific diagnosis of organic heart disease was based. In these cases, the more serious diagnosis was counted. Hypertension was recorded as the chief diagnosis in approximately 20 cases per thousand, 3 per thousand of which were regarded as transient in type. Tachycardia was third in relative frequency among the cardiovascular defects recorded, but it was noted as the most important diagnosis for 13 registrants in every thousand examined and was specified as functional tachycardia in nearly one-half of these cases. The functional type of tachycardia, as well as transient hypertension, is included in the miscellaneous group of cardiovascular defects shown in Table III.

Cardiovascular defects were noted more often for white than for Negro registrants. Of the specific defects, the valvular heart disease group was almost equally important in the two races. Cases diagnosed as being rheumatic in origin, however, occurred almost three times as often among the white registrants as they did among Negroes.

Of all the registrants who were rejected for cardiovascular defects during peacetime, almost one-half had valvular heart disease. Approximately 3 in 10 had hypertension as the principal cause for rejection. No other single defect approached this relative importance among cardiovascular rejections, the nearest being tachycardia, which accounted for about one in 12 of the cardiovascular rejections.

The importance of the various cardiovascular defects as causes for rejection of white registrants was similar to that of all races. Among Negroes, however, hypertension assumed first place, accounting for 4 in every 10 Negro cardiovascular rejections.

The changes in examining procedure which began in 1942 resulted in important changes in the diagnoses of specific cardiovascular defects. The first of these, resulting from the routine psychiatric examination at induction stations, produced a shifting of diagnoses from the cardiovascular to the psychiatric category. Thus, conditions which during peacetime were recorded by local board physicians simply as tachycardia were diagnosed by psychiatrists as paroxysmal

*Acute rheumatic fever was found infrequently among Selective Service registrants, since men with this condition seldom came up for physical examination until the acute stage had subsided. It was diagnosed in 0.1 per thousand registrants examined during 1940 and 1941, probably through affidavits from the registrants' personal physicians.

tachycardia or neurocirculatory asthenia. The prevalence of tachycardia (including functional) decreased by almost one-third under this procedure, while that of paroxysmal tachycardia and neurocirculatory asthenia tripled between 1940 and 1944.

The second change, occasioned by the routine blood pressure readings at induction stations, affected the relative importance of the specific defects within the cardiovascular group. As hypertension was diagnosed more frequently, it increased both in recorded prevalence and in importance as a principal cause for rejection, and there was a corresponding decrease in most of the other specific defects.

A third factor which affected the prevalence date for cardiovascular defects in wartime was that fewer minor heart disturbances appeared in the physician's summary of defects from which the wartime figures were obtained. This largely accounted for the decrease in recording of all heart defects from the peacetime figure of 83 to the wartime figure of 51 per 1,000 examined.[1] The relative importance of the more serious defects, however, was approximately the same as during peacetime.

Hypertension and valvular heart disease were the defects most frequently found, the former in 18.4 cases per thousand examined and the latter in 16.5 (Table IV). Tachycardia, next in frequency, was tabulated in only 4.5 cases per thousand.

Cardiovascular defects occurred in 50 of every thousand white registrants examined and in 58 per thousand Negroes. This higher rate of prevalence among the Negroes reflects the more frequent diagnoses of hypertension for that race.

TABLE IV. PREVALENCE OF CARDIOVASCULAR DEFECTS AND PERCENTAGE DISTRIBUTION OF REJECTIONS FOR THESE DEFECTS AMONG REGISTRANTS PHYSICALLY EXAMINED AT LOCAL BOARDS AND INDUCTION STATIONS, 1942-1943

MAJOR SUBGROUP	PREVALENCE PER 1,000 EXAMINED			PERCENTAGE DISTRIBUTION OF REJECTIONS		
	ALL RACES	WHITE*	NEGRO	ALL RACES	WHITE*	NEGRO
Total cardiovascular	51.0	49.8	57.7	100.0	100.0	100.0
Rheumatic and valvular	16.5	16.6	16.2	44.7	46.6	36.5
Hypertension, arterial	18.4	16.7	27.5	35.5	32.8	47.3
Tachycardia, persistent	4.5	4.8	2.7	6.1	6.7	3.5
Cardiac hypertrophy	1.8	1.7	2.7	3.6	3.3	4.5
Cardiac arrhythmia	0.6	0.6	0.5	0.3	0.4	0.3
Cardiovascular diseases, other†	2.4	2.4	2.3	5.9	6.3	4.2
Functional murmurs	3.6	3.8	2.8	0.3	0.3	0.2
Other cardiovascular defects‡	3.2	3.2	3.0	3.6	3.6	3.5

*Includes all races other than Negro.

†Includes diseases of the heart and vascular system in which the physician recorded a diagnosis other than rheumatic heart disease, valvular heart disease, hypertension, hypertrophy, tachycardia, or arrhythmia.

‡Includes entries describing signs, symptoms, or diseases of the heart and circulatory system not elsewhere classifible, such as: bradycardia, arteriosclerosis, arterial hypotension, and hypertension or tachycardia described as nervous or functional in type.

Cardiac hypertrophy was the only other cardiovascular defect recorded more frequently for Negro than for white registrants.

As in peacetime, the most important causes for rejection were the valvular heart disease group and arterial hypertension. These two defects accounted for 80 per cent of the wartime cardiovascular rejections. The two defects combined were less important for white registrants than for Negroes, but the diagnosis of valvular heart disease was far more important among the white race and that of hypertension was more important among the Negroes. Tachycardia accounted for relatively one-half as many Negro as white rejections for cardiovascular defects.

CARDIOVASCULAR SYPHILIS AND VARICOSE VEINS

Cardiovascular defects described as due to syphilis have been included in the syphilis category rather than under cardiovascular defects in Selective Service data. However, the prevalence of cardiovascular defects in which syphilis was specified as the etiology was low during both the peacetime and the wartime periods. The incidence was 0.3 per thousand registrants examined for all races, 0.1 for whites, and 1.7 for Negroes. It accounted for only 0.1 per cent of the rejections during each period.

Varicose veins were noted in 32 registrants of every thousand examined during 1940 and 1941, but during wartime they were included in the summary by induction station examiners in only 16 cases per thousand. They were responsible for little more than 1 per cent of the rejections.

CARDIOVASCULAR REJECTIONS IN RELATION TO AGE

Rejection rates for cardiovascular defects increased with increasing age. The relative importance of specific diagnoses as causes for rejection, however, differed in the various age groups. This is illustrated in Table V, which indicates the relative importance of the three leading cardiovascular diagnoses among registrants rejected in 1944.

Hypertension and valvular heart disease were almost equally important among all registrants rejected for cardiovascular defects; each accounted for more than 4 in every 10 of these rejections. Tachycardia accounted for less than one in 10 cardiovascular rejections.

A review of the percentages of rejections for the specific defects in the various age groups shows that hypertension increased sharply with increasing age; that valvular heart disease was less than one-half as important among men 30 years of age and over as among the 18-year-old registrants; and that the proportion rejected for tachycardia was relatively constant in each age group.[2]

Hypertension was the only cardiovascular subgroup of less relative importance as cause for rejection of white registrants than of all races; for Negroes, it was the only defect more important for them than for all races. It accounted for 40 per cent of the white as compared to 67 per cent of the Negro cardiovascular rejections.

TABLE V. PERCENTAGE OF CARDIOVASCULAR REJECTIONS DUE TO SPECIFIC DIAGNOSES, BY AGE AND RACE*

AGE (YR.)	TOTAL	PERCENTAGE OF CARDIOVASCULAR REJECTIONS FOR			
		ARTERIAL HYPERTENSION	RHEUMATIC AND VALVULAR HEART DISEASE	TACHY-CARDIA	OTHER
		All Races			
All ages	100.0	43.7	42.4	6.7	7.2
18	100.0	14.0	69.4	6.1	10.5
18-25	100.0	35.5	49.2	8.0	7.3
26-29	100.0	44.1	43.7	6.3	5.9
30 and over	100.0	52.7	33.8	6.4	7.1
		White†			
All ages	100.0	38.9	45.7	7.7	7.7
18	100.0	9.5	72.7	6.5	11.3
19-25	100.0	28.9	54.4	9.0	7.7
26-29	100.0	38.8	47.6	7.4	6.2
30 and over	100.0	48.8	36.4	7.3	7.5
		Negro			
All ages	100.0	67.0	26.0	2.2	4.8
18	100.0	39.8	51.1	3.4	5.7
19-25	100.0	61.8	29.0	3.8	5.4
26-29	100.0	67.5	26.6	1.5	4.4
30 and over	100.0	74.8	19.4	1.3	4.5

*Based on a sample of Reports of Physical Examination and Induction for registrants inducted or rejected during February, 1944, through May, 1944.

†Includes all races other than Negro.

In general, the distribution of the various cardiovascular defects as causes for rejection in each racial category followed the same trends as for all races. Hypertension increased in relative importance with increasing age; valvular heart disease decreased sharply as age increased, and tachycardia decreased only slightly.

OCCUPATIONS OF CARDIOVASCULAR REJECTEES

The occupational distribution of registrants rejected because of cardiovascular defects is shown in Table VI. Selective Service policies regarding occupational deferments affect the representativeness of certain of these major occupational groups, however, notably the farm owners and farm laborers. Their physical and mental defects are probably less representative of the farmers in the general population than of those in other occupations, since the Tydings Amendment to the Selective Training and Service Act late in 1942 resulted in widespread occupational deferments in the agricultural groups, without physical examination.

TABLE VI. PERCENTAGE OF REJECTIONS IN MAJOR OCCUPATIONAL GROUPS BASED ON CARDIOVASCULAR DEFECTS*

OCCUPATION	PERCENTAGE OF REJECTIONS IN EACH OCCUPATION GROUP DUE TO CARDIOVASCULAR DEFECTS		
	ALL RACES	WHITE†	NEGRO
All occupations	9.2	9.2	9.3
Professional and semiprofessional	12.1	12.1	‡
Farm owners, managers, and laborers	6.9	6.9	6.8
Proprietors, managers, and officials	12.7	12.7	‡
Clerical, sales, and kindred	11.5	11.4	‡
Craftsmen and foremen	9.9	9.8	12.3
Operatives	9.5	9.2	11.6
Service workers	10.5	10.5	‡
Laborers, except farm	7.9	6.4	9.9
Students	15.1	14.8	‡
Emergency workers and unemployed	4.7	5.0	3.9
Nonclassifiable and not stated	7.2	7.2	7.2

*Based on a sample of Reports of Physical Examination and Induction for registrants examined during February, 1944, through April, 1944.

†Includes all races other than Negro.

‡Negro rates not presented for occupations with less than 2 per cent of total Negro rejections.

Cardiovascular defects accounted for 9 per cent of the rejections in all occupations, with approximately the same proportions of white and Negro rejections made for these defects. Only three occupational groups, the farm owners and laborers, other laborers, and the emergency workers and unemployed, had relatively fewer cardiovascular rejections than the average for all occupations.

Students had the highest proportion of rejections for cardiovascular defects. These were the principal defects of almost one in every 6 of the student rejections. Approximately one in every 8 rejections in the professional group and in the managerial and official group were made because of cardiovascular defects. Among emergency workers and the unemployed, at the lowest extreme, only one in 20 was rejected for cardiovascular defects.

Among white registrants, cardiovascular rejections in each occupational group were similar to those for all registrants. Relatively more Negro than white registrants who were craftsmen and foremen, operatives, and laborers were rejected for cardiovascular defects.

RE-EXAMINATION OF REGISTRANTS WITH CARDIOVASCULAR DEFECTS

Early in Selective Service experience the question arose as to whether any considerable number of men who had been found disqualified for military service might have been rejected on mistaken diagnoses. In order to determine the probable amount of salvage of such men, and also to make possible a detailed analysis of current problems in cardiovascular diagnosis, a re-examination study was made by special medical advisory boards in five of the largest cities in

the country. This study, covering re-examination of 4,994 men formerly rejected because of cardiovascular defects and neurocirculatory asthenia, was conducted by members of the Subcommittee on Cardiovascular Diseases, National Research Council, who were appointed as members of special Selective Service Medical Advisory Boards.[3]

Of the 4,994 men who were re-examined, 17.3 per cent were resubmitted as qualified for general military service, while the remaining 82.7 per cent were retained in the rejected classification. In view of the relatively small percentage of registrants reclassified for induction, the time required for re-examination, and the scarcity of expert examiners during wartime, the wisdom of extending the re-examination of registrants rejected for cardiovascular defects was considered doubtful.

The five leading causes for rejection, in order of their importance, were: rheumatic heart disease, found on first examination in 50 per cent of the total 4,994, and diagnosed for 59.9 per cent of those rejected after re-examination; arterial hypertension; neurocirculatory asthenia; sinus tachycardia; and congenital heart disease.

Several problems in diagnosis raised by the study were posed for further research, possibly in a follow-up of the borderline cases. Chief among these were questions of (1) interpretation and significance of apical systolic murmurs; (2) the possible need for extending the upper limits of blood pressure standards in very nervous young men to 160 mm. or slightly higher, provided the diastolic pressure does not exceed 90 mm.; extending the limits of pulse rates at rest to approximately 40 to 120 per minute; and expanding the limits on heart size. The usefulness of exercise tests in cardiovascular examination for military service was also questioned.

SUMMARY

Some of the more important facts derived from Selective Service experience in the physical examination of men with cardiovascular defects may be summarized as follows:

1. Cardiovascular defects are among the leading causes for rejection of Selective Service registrants. Among men in the rejected classes, they are the fourth group in order of importance, exceeded only by mental disease, mental deficiency, and musculoskeletal defects.

2. More than 300,000 registrants, or 6.7 per cent of the total in the rejected classes on Jan. 1, 1945, had heart defects as the most serious defect. The percentage of white registrants with these defects was larger than that of Negroes.

3. Valvular heart disease (rheumatic and syphilitic) and arterial hypertension have been the leading specific causes for cardiovascular rejection, as well as the most frequently recorded cardiovascular defects, during both peacetime and wartime. Valvular heart disease occurred more frequently among white registrants, while hypertension was a much more important diagnosis among the Negroes.

4. Within the various age groups, rejections for rheumatic-valvular heart disease decreased as age increased; it was particularly important among 18-year-old registrants, accounting for nearly 70 per cent of their cardiovascular rejections during a four-month period in 1944.

5. Arterial hypertension became more important as a cause for rejection with increasing age. Among registrants 30 years old and over who were rejected because of cardiovascular defects it accounted for more than one-half the rejections. Less than one-half the white rejections 30 years of age and over were made for this cause, however, while three-fourths of the Negroes in this age group who were rejected for cardiovascular defects had arterial hypertension.

6. Emergency workers, the unemployed, and farmers had the lowest percentages of rejections for cardiovascular defects; students had the highest percentage of rejections for these defects.

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Clinical Reports

ACUTE PERICARDITIS SIMULATING CORONARY ARTERY OCCLUSION

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ACUTE pericarditis of infectious origin may present various clinical patterns. Its existence is often undetected because the symptoms and signs are weighed with those of the underlying disease. Occasionally, its onset is manifested by severe precordial pain and shock, simulating an acute coronary occlusion. Cases of this type have been described by Barnes and Burchell.[1] Differentiation between the two conditions is, of course, important because of the difference in their management and prognosis. In a recent small series of cases of acute pericarditis simulating coronary occlusion which were reported by Wolff,[2] mention was made of the presence of a slow pulse as a differentiating feature of pericarditis. Recently we saw a patient with severe precordial pain, shock, and slow pulse in whom myocardial infarction was suspected but in whom further study led to a diagnosis of acute pericarditis. The case is presented because this particular clinical picture is not well known.

CASE REPORT

A 26-year-old Army officer came to the hospital at 8 A.M. on Oct. 5, 1944, with the presenting symptom of intense substernal pain which had awakened him three hours earlier. The pain radiated to both shoulders, was aggravated by breathing, and prevented him from assuming a recumbent position. He had previously been in good health and there was no history suggesting that he had ever had rheumatic fever, tuberculosis, coronary insufficiency, trauma to the chest, or a recent respiratory infection.

Preliminary examination revealed a young man who did not appear ill except that he was unable to lie flat on the examining table because of pain in the anterior midchest. No abnormality of the heart, lungs, or thoracic wall could be detected. The blood pressure was 120/80 and the heart rate, 72 per minute. During the examination a sudden and dramatic change occurred in the appearance of the patient. The face became ashen and the lips cyanotic. The heart rate fell to 38 per minute, the rhythm became irregular, and the sounds almost inaudible. The blood pressure could not be measured. The skin became covered with a cold, drenching sweat. This alarming situation improved gradually after the administration of morphine sulfate. The pulse slowly increased to 60 per minute and the blood pressure to 90/60. The patient was transferred to a hospital bed where he was placed in a sitting position and in an oxygen tent. Two more doses of morphine were necessary to control the pain which remained severe until noon. Six hours after admission the patient was completely free of pain and could lie flat without dis-

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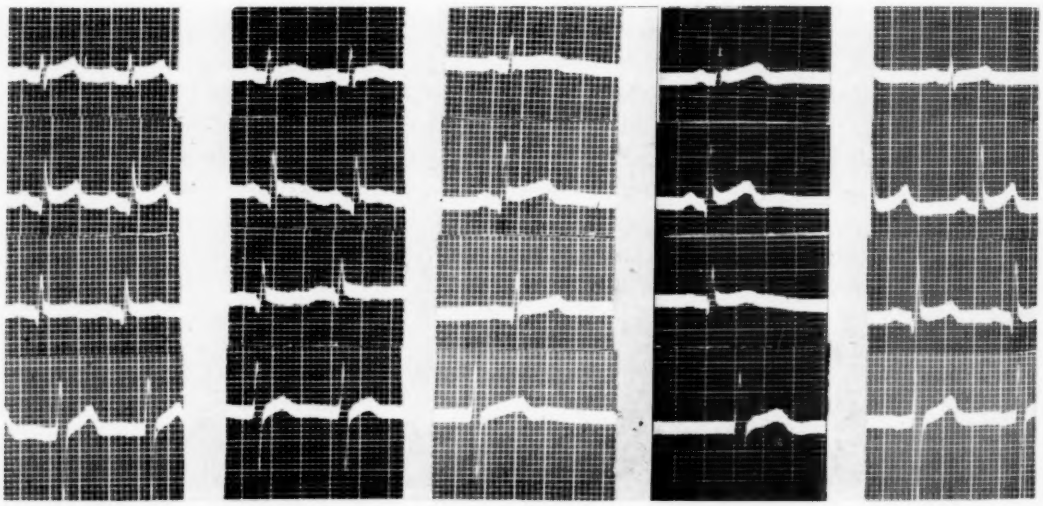
comfort and without the use of oxygen. He presented a normal appearance. The heart sounds were clearer, the rate was 80 per minute, the rhythm was regular, and the blood pressure was 120/80. This respite, however, was brief, and a few hours later cyanosis reappeared, the heart rate increased to 130 per minute, and the temperature rose to 100° Fahrenheit. Fortunately resumption of oxygen therapy was followed by an amelioration of symptoms after several hours. The following morning the temperature, pulse rate, and blood pressure reached normal levels where they remained for the duration of the patient's hospital stay. At this time a pericardial friction rub became audible over the lower sternum. The friction rub disappeared in several hours and made its final appearance the following day for a short time. The further course of the patient was uneventful. No evidence of pericardial effusion or cardiac enlargement was observed. The patient was kept in bed for four weeks and returned to his usual duties after a short convalescent leave.

The leucocyte count was 16,700 on the day of admission, 12,150 on the following day, and subsequently normal. The blood sedimentation rate by the Westergren method was 64 mm. in one hour and did not approach normal limits until the twelfth hospital day. The most important laboratory findings were revealed by the electrocardiograms. As will be seen in Fig. 1, *A*, the S-T segments are slightly elevated in Leads I and II without reciprocal S-T_3 deviation. Small



A. *B.* *C.* *D.* *E.*

Fig. 1.—The electrocardiograms consist of the three standard limb leads and Lead CR_4. The findings are discussed in the text. *A*, Taken Oct. 5, 1944; *B*, Oct. 6, 1944; *C*, Oct. 9, 1944; *D*, Oct. 13, 1944; *E*, March 3, 1945.

Q_2 and Q_3 waves are present. In Fig. 1, *B*, elevated S-T segments are present in all limb leads and the T waves in all leads are of lower amplitude. Lead CF_4 is normal. *C* and *D* of Fig. 1 are representative of subsequent electrocardiograms and show no changes characteristic of myocardial infarction, the only abnormality present being S-T segment elevation in the indirect leads.

Spontaneous mediastinal emphysema or pneumothorax as a cause of the clinical picture[3] and electrocardiographic changes[4] were precluded by the normal roentgoenograms of the chest and the absence of relevant clinical findings.

Approximately six months after the onset of the illness, the patient appeared for a routine examination. He had been asymptomatic throughout this period of time. Physical examination of the heart revealed no abnormalities. Roentgen examination of the heart was likewise normal. An electrocardiogram taken at this time (Fig. 1, *E*) showed that slight elevation of the S-T segments in Leads II and III was still present.

COMMENT

At the time the patient had severe substernal pain, shock, and cyanosis, he appeared critically ill. It is natural to associate this picture with an acute myocardial infarction. Criteria favoring a diagnosis of acute pericarditis, however, were present and included the youth of the patient. A significant characteristic of the pain was its aggravation by breathing and change of position. This rarely occurs in infarction of the myocardium. The slow pulse rate mentioned by Wolff[2] was also present. The transitory friction rub and fever were more suggestive of myocardial infarction than pericarditis because in the latter condition these signs tend to be present from the onset and are more persistent. Finally, the electrocardiographic changes were characteristic of acute pericardities.[1]

Collapse with slow pulse and low blood pressure may have been the result of increased vagal tone caused by the pericarditis or by the pleuritis which is frequently associated with it. A similar reflex vagal stimulation is occasionally observed following puncture of the chest wall (so-called pleural shock) or during abdominal operations.

The presence of fever, leucocytosis, and an elevated blood sedimentation rate was considered evidence for an infectious origin of the pericarditis. No specific etiologic factor, however, was present. Rheumatic fever, tuberculosis, septicemia, uremia, and disseminated lupus erythematosus are usually revealed by clinical characteristics not present in the case described. Barnes and Burchell[1] have observed young adults with a benign and apparently limited form of pericarditis possibly caused by tuberculosis. Acute pericarditis may be associated with infections of the upper respiratory tract[5] and sinuses[6] and may complicate primary atypical pneumonia.[7] It has also been described following operative procedures[8,9] and in epidemic form.[10] In one series of cases,[1] evidence of an upper respiratory tract infection was found in 57 per cent of patients. In the remaining 43 per cent, as in our case, no causative agent was demonstrated.

CONCLUSION

A case report of acute pericarditis of unknown etiology is presented to illustrate that the clinical picture may be one of intense precordial pain associated with shock and a strikingly slow pulse. Vagal stimulation of reflex nature from the inflamed pericardium is suggested as the cause of the collapse and slow pulse. Acute pericarditis may closely simulate acute coronary occlusion.

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BILATERAL PULMONARY INFARCTION AND PNEUMOTHORAX COMPLICATING HYPERTENSIVE, CORONARY HEART DISEASE WITH MYOCARDIAL INFARCTION: REPORT OF A CASE

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SPONTANEOUS pneumothorax has been reported in association with a number of clinical conditions, including tuberculosis, pneumonia, and bronchial asthma, and secondary to mediastinal emphysema. Marks[1] has observed pneumothorax secondary to pulmonary infarction. According to Hamman,[2] spontaneous pneumothorax may be produced by any of four mechanisms: (1) rupture of subpleural blebs, (2) a rent in the pleura due to pull of adhesions, (3) rupture into the pleura of congenital pulmonary cysts, or (4) mediastinal emphysema with rupture of the mediastinal pleura. He expressed the opinion that, when bilateral spontaneous pneumothorax is present, mediastinal emphysema must precede the pneumothorax.[3]

It is the purpose of this paper to report a case of bilateral spontaneous pneumothorax associated with pulmonary infarction and myocardial infarction. Other features of clinical interest in the case were the marked increase of the diastolic blood pressure after renal infarction and the absence of further intracardiac or peripheral manifestations of vascular thrombosis after the institution of dicumarol.

REPORT OF A CASE

The patient was a white man, 44 years of age, examined first Dec. 14, 1944. He complained chiefly of dyspnea and cough. He stated that four weeks previously he had been seized with severe substernal thoracic pain, which extended to the left shoulder and elbow. Morphine was necessary for relief. Part-time rest in bed had been instituted for two weeks. Although dyspnea and cough had made their appearance, he then had been permitted to resume light activity. This had been accompanied by increased shortness of breath and hemoptysis. The twenty-four hours prior to the first examination had been spent on the train, with symptoms increasing in intensity. Nausea and vomiting were present also.

The past history revealed hypertension of ten to twelve years' duration. The blood pressure had ranged from 200/100 to 210/110. There was no history of rheumatic fever, scarlet fever, chorea, or recurrent sore throats.

The results of physical examination revealed a severely dyspneic, cyanotic, acutely ill white man. The pulse rate was 140 beats per minute; the blood pressure was 150/100; the temperature was 100.2° Fahrenheit. There were restricted expansion and posterior dullness to percussion of the right portion of the thorax. Râles were present over the right portion of the thorax anteriorly and posteriorly. A protodiastolic gallop rhythm was present at the apex. No murmurs were heard. The edge of the liver was palpable one fingerbreadth below the costal margin.

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Examination of the urine revealed specific gravity, 1.021; pH, 4.5; albumin, Grade 2 (on the basis of 1 to 4 in which 1 represents the least and 4 the greatest amount of albumin); sugar, negative; and 2 to 4 leucocytes per high-power field. Erythrocytes numbered 5,090,000, and leucocytes, 17,400 per cubic millimeter of blood. The concentration of hemoglobin was 95 per cent (Sahli). The percentages of the various types of leucocytes were as follows: polymorphonuclears, 73; staff cells, 7; eosinophils, 2; lymphocytes, 15; and monocytes, 3. The electrocardiogram was interpreted as consistent with anterior myocardial infraction (Fig. 1). Roentgenographic examination of the thorax revealed elevation of the right side of the diaphragm. There were mottled shadows throughout the entire right pulmonary field with a large circular shadow of increased density in the region of the right middle lobe (Fig. 2). The left side of the thorax showed extensive mottling throughout. Both costophrenic sinuses were clear. The transverse diameter of the thorax measured 31 cm., and that of the heart was 16 centimeters. The findings were interpreted as being consistent with pulmonary infarction, but bronchopneumonia could not be excluded.

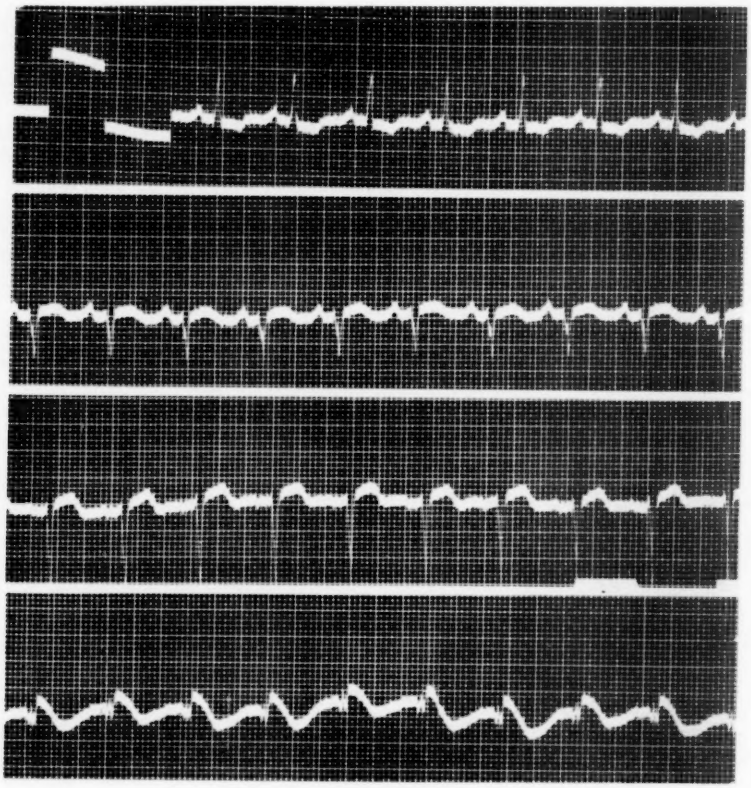

Fig. 1.—Electrocardiogram consistent with anterior myocardial infarction.

Routine measures for treatment of congestive heart failure, including administration of digitalis and complete rest in bed, were begun. Penicillin was likewise administered in view of fever, leucocyte count, and roentgenographic examination. Administration of 15,000 units of penicillin every third hour was continued for seven days. There was improvement of dyspnea and cough, and in three days the temperature had returned to normal. By December 19 the gallop rhythm had disappeared and leucocytes numbered 11,700 per cubic millimeter of blood,

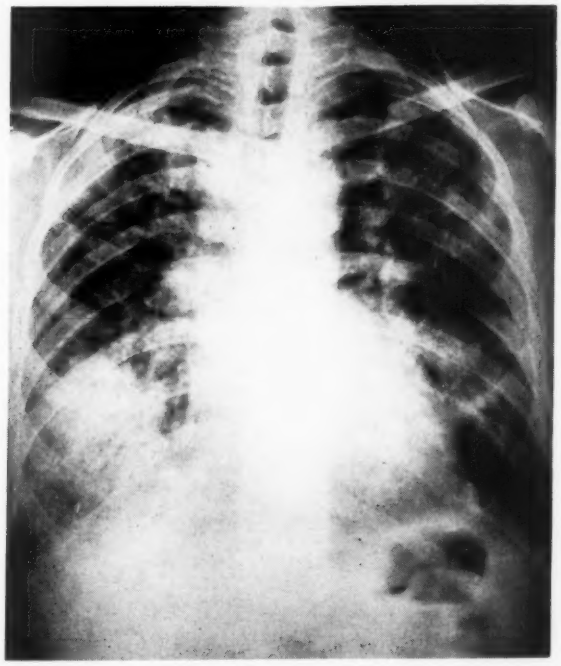

Fig. 2.—Bilateral pulmonary infarcts.

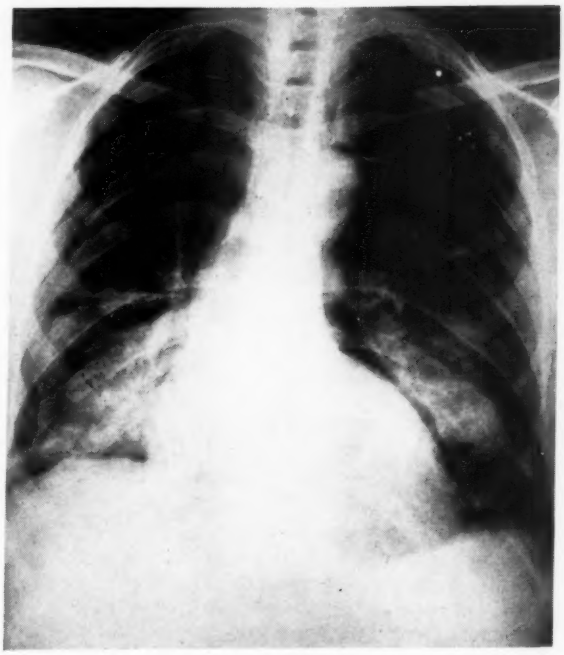

Fig. 3.—Bilateral pneumothorax and bilateral pulmonary infarcts.

with 83 per cent polymorphonuclears. Beginning December 21, however, there was an elevation of temperature for two days to 101 to 102° Fahrenheit. The cough became more severe on December 23 and was accompanied by severe pain in the right side of the thorax without further elevation of temperature. Roentgenographic examination of the thorax now revealed bilateral pneumothorax with severe passive congestion in both pulmonary fields and probable regions of infarction in the inferior lobes (Fig. 3). Since dyspnea was increased as a result of the bilateral spontaneous pneumothorax, oxygen was administered by means of a tent for three days.

There appeared to be gradual improvement until December 30, when there was observed sudden severe pain in the upper right quadrant of the abdomen, extending to the right flank and groin. There was sudden elevation of temperature to 102° F., and leucocytes numbered 25,050 per cubic millimeter of blood, with 89 per cent polymorphonuclears. Analysis of the urine revealed albumin, Grade 4, with many hyaline and granular casts. A diagnosis of infarction of the right kidney, probably secondary to embolization of the right renal artery, was made. The condition of the patient became critical with temperature rising to 102° F. and pulse rate to 150 beats per minute. Protodiastolic gallop rhythm reappeared. There was a transient drop of blood pressure to 140/90, but subsequent determinations revealed pressures ranging from 170/130 to 180/140. Nausea and vomiting reappeared and abdominal distention developed.

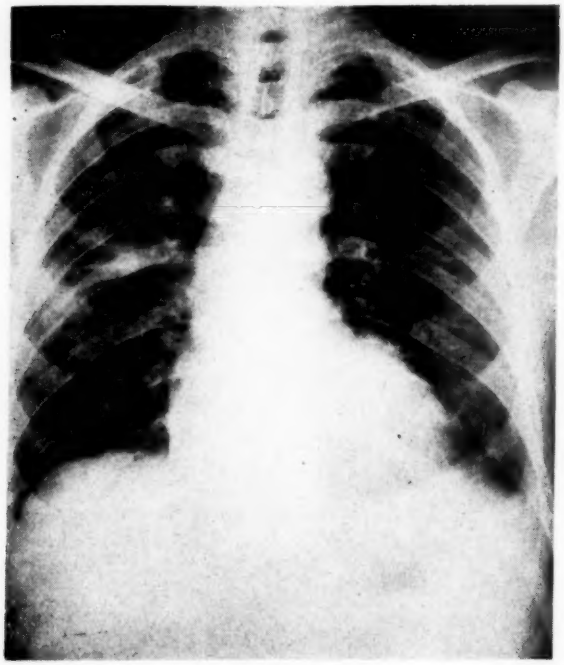

Fig. 4.—Clear lung fields.

By Jan. 6, 1945, there was improvement, with disappearance of nausea, vomiting, and abdominal distention. Dyspnea and cough were less troublesome. The temperature returned to normal, and the pulse rate ranged from 90 to 100 beats per minute. Roentgenographic examination of the thorax Jan. 19, 1945, revealed complete resolution of the multiple infarcts and both lungs were fully expanded (Fig. 4). There were a decrease of the size of the heart and considerable decrease of the passive congestion. The condition of the patient at this time had improved to such an extent that he was dismissed from the hospital.

For the next two months the patient was examined at frequent intervals. Administration of digitalis and ammonium chloride, restricted intake of fluid, and limited activity were con-

tinued. The dyspnea and cough did not completely disappear, and toward the end of this period of observation they increased in severity. These symptoms were now accompanied by painful enlargement of the liver, and edema of the ankles appeared for the first time. These manifestations of right heart failure developed rapidly so that the patient was readmitted to the hospital March 14, 1945.

The results of re-examination revealed pulse rate, 100 beats per minute; temperature 98° F.; and blood pressure, 170/140 to 176/150. Protodiastolic gallop rhythm was present. The second sound at the pulmonic area was louder than at the aortic area. No murmurs were present. The liver was palpated for a distance 5 cm. below the right costal margin. Grade 2 edema of the ankles was present.

Complete rest in bed was instituted and the same medication was continued. In view of the previous pulmonary infarctions, dicumarol therapy was instituted, maintaining the prothrombin time (Quick method) between thirty-five and sixty seconds. As nausea was still severe, lanatosid-C was substituted for digitalis. Roentgenographic examination of the thorax revealed passive congestion in both pulmonary fields. The transverse diameter of the heart had increased to 20.5 centimeters. On analysis of the urine the albumin was found to be Grade 4 with 16 to 18 hyaline and 7 to 10 granular casts per high-power field. The concentration of nonprotein nitrogen was 45.5 mg. per 100 c.c. of serum.

Increasing dyspnea developed and administration of mercurphylline injection (mercupurin) was started. Satisfactory diuresis occurred; at times as much as 3,500 to 4,000 c.c. of urine in twenty-four hours was obtained after the intravenous administration of 1 c.c. of mercurphylline. The manifestations of right heart failure continued and pleural effusions developed bilaterally. On April 9, 1945, 2,500 c.c. of amber-colored fluid was obtained by right thoracentesis. Subsequently, thoracentesis was done as follows: April 11, left (1,700 c.c.); April 15, right (2,000 c.c.); April 22, left (1,700 c.c.). There was only slight improvement of symptoms. Death occurred suddenly on April 23, 1945, 130 days after the first examination.

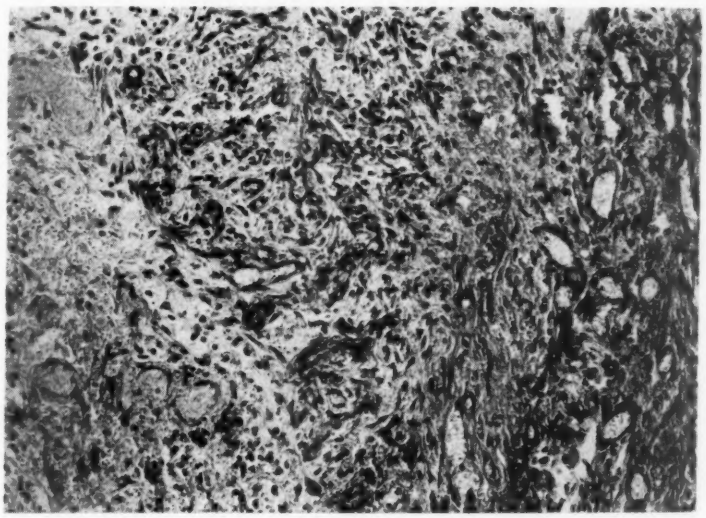

Fig. 5.—Lung at the edge of the infarct with fibroblasts and newly formed capillaries (× 125).

At necropsy the following observations were deemed significant: The heart was moderately enlarged and weighed 600 grams. The right ventricular wall measured 6 mm. and the left ventricular wall measured 20 mm. in thickness. The left ventricular wall in the anterior apical region was thinned to a width of 2 to 3 mm. with formation of an aneurysm. There was an old, well-

organized thrombus in the left ventricle, measuring 6 by 5 by 2 cm. and firmly adherent to the endocardium beneath the aneurysm. Smaller old mural thrombi were present in the right ventricle between the trabeculae carneae. The valves were normal.

The coronary sclerosis of the left circumflex and the right coronary arteries was Grade 2. The sclerosis of the left anterior descending coronary artery was Grade 3 and the artery was occluded by an old ante-mortem thrombus which originated 1.0 cm. from the bifurcation of the left coronary artery.

There was approximately 1,000 c.c. of amber-colored fluid in each pleural cavity. Over the right middle lobe there was a small pleural cyst, measuring 1.5 by 1.0 by 1.0 cm. and containing an organized blood clot. The right lower lobe was atelectatic and contained an organized infarct

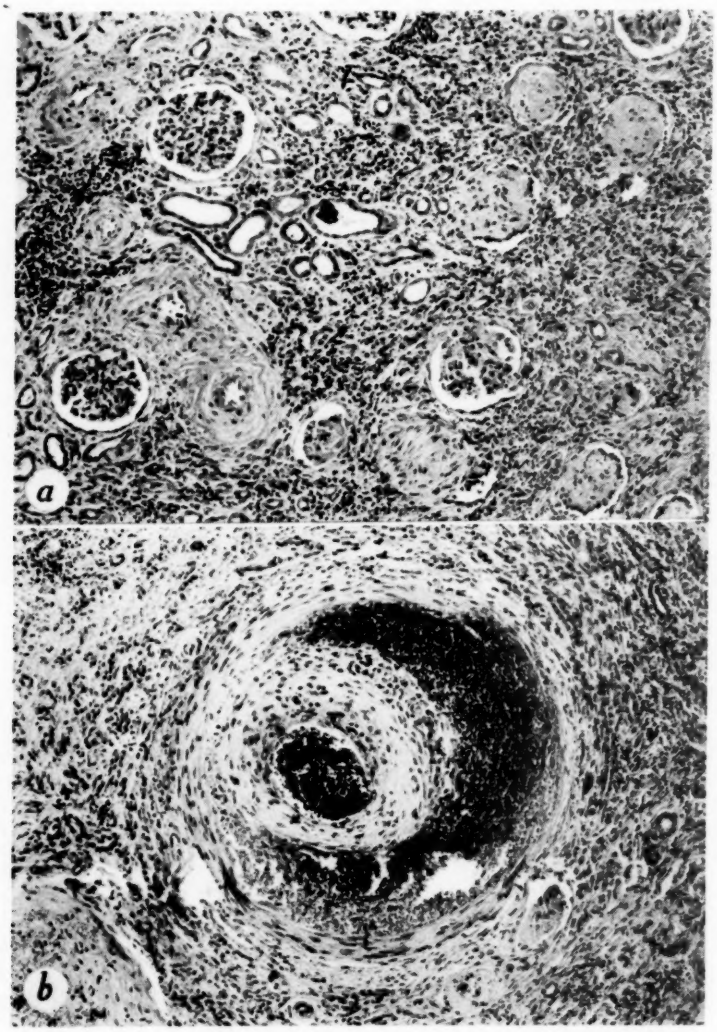

Fig. 6.—Right kidney. *a*, Hyalinized glomeruli, increased interstitial tissue, lymphocytes, and marked medial thickening of small arteries (× 90). *b*, Medium-sized artery with dissecting hemorrhage in the media (× 90).

measuring 4.0 by 4.0 by 3.0 centimeters. Smaller infarcts were present in the right middle lobe and the left lower lobe. There were well-organized thrombi in the pulmonary arteries leading to the right middle and lower lobes and left lower lobe.

In the liver there was the nutmeg appearance of chronic passive congestion.

The right kidney was atrophic and weighed 45 grams. More than three quarters of its parenchyma was destroyed by old and recent infarcts. The left kidney was hypertrophied and weighed 325 grams. The right renal artery was narrowed by atherosclerotic plaques and measured 0.5 cm. in circumference, whereas the left renal artery measured 1.5 cm. in circumference. No thrombi were found in the renal arteries.

Histologic Examination.—In sections of the left ventricle at the site of aneurysm, there was no normal myocardium. Most of the myocardium had been replaced by fibrous connective tissue. A few regions contained old degenerating muscle fibers without nuclei; these fibers were surrounded by fibroblasts. In some regions there were newly formed capillaries. There was a firmly adherent mural thrombus attached to the endocardium.

There was marked atherosclerosis in the left anterior descending coronary artery. The lumen was partially occluded by an old organized thrombus undergoing organization and recanalization. In the center there was a recent ante-mortem thrombus which completely occluded the lumen.

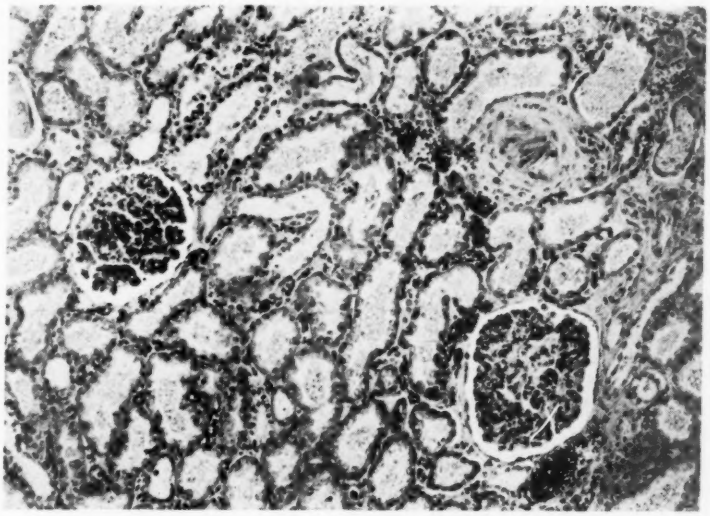

Fig. 7.—Left kidney. Normal glomeruli, tubules, and interstitial tissue with moderate medial thickening of small artery (× 90).

In all sections of the lung the alveoli contained large numbers of pigment-laden macrophages. In some regions the alveoli were also filled with erythrocytes and pink-staining edema fluid. There was medial hypertrophy of the small and medium-sized pulmonary arteries. Small foci of organization were present, and in a few sections overgrowth of the alveolar epithelium was seen. There was squamatization of bronchial epithelium in several sections. In the right middle and lower lobes and left lower lobe old pulmonary infarcts were seen. Organization at the edges of the infarcts was present, as manifested by granulomatous reaction with fibroblasts and newly formed capillaries (Fig. 5). The pleural cyst over the right middle lobe contained ghosts of erythrocytes and fibrin. A granulomatous reaction was present at the edge of the organized blood clot.

In the liver the sinusoids in the region of the central veins were congested and filled with erythrocytes. In the same location foci of necrosis were present.

The sinusoids of the spleen were congested and filled with erythrocytes. There was marked hyalinization of the arterioles.

In the right kidney there were numerous regions of old and recent infarction. In the few remaining regions of renal tissue there was marked atrophy with increase of interstitial tissue, lymphocytes, atrophic tubules, and hyalinized glomeruli (Fig. 6, *a*). Marked medial hypertrophy was present in arteries and arterioles. In one medium-sized artery there was a dissecting hemorrhage into the wall of the media (Fig. 6, *b*).

In sections of the left kidney, the glomeruli, tubules, and interstitial tissue appeared normal. Medial hypertrophy was present but to a lesser degree than that seen in the right kidney (Fig. 7).

The following anatomic diagnoses were made: Hypertrophy of the heart (600 grams); coronary sclerosis Grade 2 to 3 with old thrombosis of the left anterior descending coronary artery; myocardial infarction (old) of the anterior and apical surfaces of the left ventricle with formation of aneurysm; mural thrombi (old) of right and left ventricles; thrombosis (old) of the branches of the pulmonary artery to the right middle and lower lobes and left lower lobe; chronic passive congestion of the liver; arteriosclerotic occlusion of the right renal artery; old and recent infarcts of the right kidney with atrophy.

COMMENT

In the case presented, hypertensive heart disease was followed by coronary thrombosis and occlusion of the left anterior descending coronary artery, with myocardial infarction of the anterior and apical surfaces of the left ventricle. These changes in turn led to ventricular aneurysm and formation of mural thrombi in both ventricles. Embolization of the pulmonary arteries and pulmonary infarction followed. During the period of acute pulmonary infarction, bilateral spontaneous pneumothorax developed. The patient recovered from multiple pulmonary infarction with bilateral spontaneous pneumothorax, but death occurred four months later as a result of right heart failure.

In Marks'[1] discussion of pulmonary infarction and pneumothorax, he emphasized the fact that septic infarcts are more likely to give rise to pneumothorax than are uninfected infarcts and stated that, if necrosis occurs within the infarcted region and pneumothorax results, there is likely to be a rapid outpouring of purulent exudate, thus giving rise to pyopneumothorax. In the first case reported by Marks, thrombi were observed in the right pulmonary artery and small regions of consolidation were present in each lung. No further description of the lung was given. In his second case there was gangrene of the middle and lower lobes of the right lung with empyema. Histologic study of the lungs was not given in either case.

With pulmonary infarction, secondary infection of the infarcted lung is not essential for the production of pneumothorax. In the case reported, the pulmonary infarcts were probably the result of emboli originating from bland mural thrombi present in the right ventricle. The popliteal and femoral veins, however, cannot be entirely eliminated as the source of the emboli. There was no demonstrable evidence of systemic infection, the infarcts were not secondarily infected, and organization was occurring, as manifested by the granulomatous reaction at the edges of the infarcts. The histologic appearance of the pulmonary in-

farcts was consistent with the four-month history, coinciding with the bilateral spontaneous pneumothorax.

It is not possible to state the exact mechanism of formation of spontaneous pneumothorax in this case. It is possible that air may have passed directly into the pleural cavities during the period of pulmonary infarction, as suggested by Marks. It seems more logical, however, that during paroxysms of coughing, rupture of the alveoli of the lung occurred, thereby permitting passage of air into the interstitial connective tissue of the lung. This is in accord with the view of Hamman,[2] who expressed the opinion that air gaining access to the interstitial tissue of the lung travels along the pulmonary vessels until it reaches the mediastinum. The air, having reached the mediastinum, ruptures through the thin mediastinal wall into the pleural cavity. The bilateral occurrence of spontaneous pneumothorax, however, is evidence in favor of mediastinal emphysema preceding the pneumothorax.[3]

It has been reported that spontaneous mediastinal emphysema and pneumothorax may be confused with heart disease.[4] In the case reported, hypertensive heart disease and coronary heart disease with myocardial infarction coexisted with spontaneous bilateral pneumothorax. The presence of pneumothorax superimposed on pulmonary and myocardial infarction not only adds diagnostic difficulties, but also complicates therapeutic measures.

It is possible that the partial occlusion of the right renal artery with atrophy and infarction of the kidney played a role in the causation of the hypertension. The manifestations of vascular disease were more severe in the atrophic than in the hypertrophic kidney. However, it is realized that it is impossible by gross examination or histologic study of the kidneys in cases of unilateral renal disease to state that the atrophic kidney was the cause of hypertension in any specific case.[5] It was observed clinically, however, in this case that after one episode of renal infarction the diastolic blood pressure was higher than it had been before the episode. This has been recorded previously.[6,7]

Dicumarol has received much attention in the prevention of intravascular thrombosis. It was used in this case as a prophylactic measure five weeks prior to death, with the hope of preventing any further thrombotic or embolic manifestations. During this period of administration of dicumarol, no embolic phenomena were observed, although congestive heart failure was marked. At post-mortem examination all thrombi observed in the heart and lungs were old and probably had existed prior to the beginning of dicumarol therapy.

SUMMARY

Spontaneous bilateral pneumothorax may occur in association with pulmonary infarction. Secondary infection of a pulmonary infarct is not essential for the development of pneumothorax. In the case reported, pulmonary infarction was probably secondary to ancient myocardial infarction. A rise in the diastolic blood pressure was observed clinically after one episode of renal infarc-

tion. Dicumarol was used prophylactically with the hope of preventing additional intravascular thromboses. Additional thrombotic manifestations were not observed after the administration of dicumarol in this case.

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PURPURIC MANIFESTATIONS OF RHEUMATIC FEVER AND ACUTE GLOMERULONEPHRITIS

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A VARIETY of hemorrhagic conditions, characterized by spontaneous bleeding beneath the skin, from the mucous membranes, or into the joints, have been grouped together under the term "purpura." The subcutaneous hemorrhages appear as small, discrete, purplish spots known as petechiae, or as larger splotchy, confluent areas referred to as ecchymoses. Purpura, like fever, headache, or pain, is only a sympton or manifestation of an underlying pathologic condition which in some cases is very evident but in others assumes an idiopathic nature. The present study is concerned only with simple purpura, without demonstrable blood changes, as noted in two specific conditions. Purpura of this type is a manifestation of many diseases and disorders. In some it results from mechanical causes such as venous stasis or emboli in endocarditis. In others it is due to acute infectious diseases, most notably cerebrospinal meningitis. It is also a consequence of nutritional disorders and the administration of certain drugs, particularly quinine, atropine, and the iodides.

Three cases of symptomatic purpura are presented. In two, the etiology was rheumatic fever, and in the third it was acute glomerulonephritis. The first two cases presented an unusual problem since, due apparently to pure coincidence, they were admitted to the same sick bay within six hours of each other and with nearly identical histories. A thorough search revealed no common toxic agent which might have caused this unusual circumstance. The two men worked in different places at different types of work, slept in entirely separate barracks, and ate at different mess halls. One of these cases became even more interesting when signs of renal disease became so evident that a co-existent diagnosis of both rheumatic fever and acute nephritis seemed justified.

CASE HISTORIES

CASE 1.—W. K., a 23-year-old Motor Machinist's Mate, Second Class, was admitted to the sick list Feb. 7, 1945. Three weeks previously he had had acute tonsillitis which had improved rapidly following the administration of sulfadiazine. Three days prior to admission, he began to have swelling and local heat and pain in the left knee, followed rapidly by migrating polyarthritis. The next day a red rash appeared over both lower legs, and on the day of admission he had a severe chill, followed by fever, palpitation, and generalized malaise. The past, occupational and family histories were negative as concerned rheumatic fever, allergy, or exposure to toxic agents.

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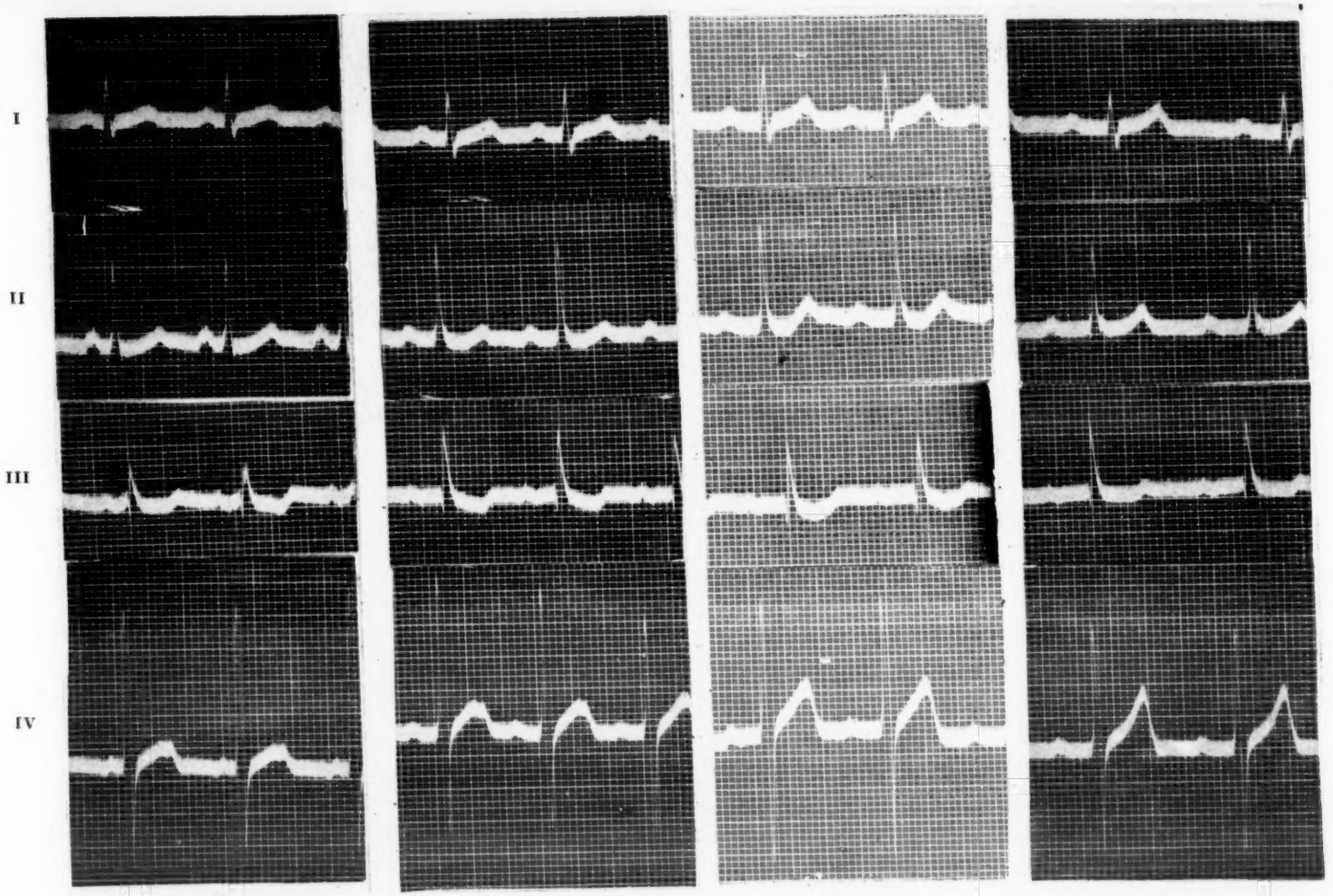
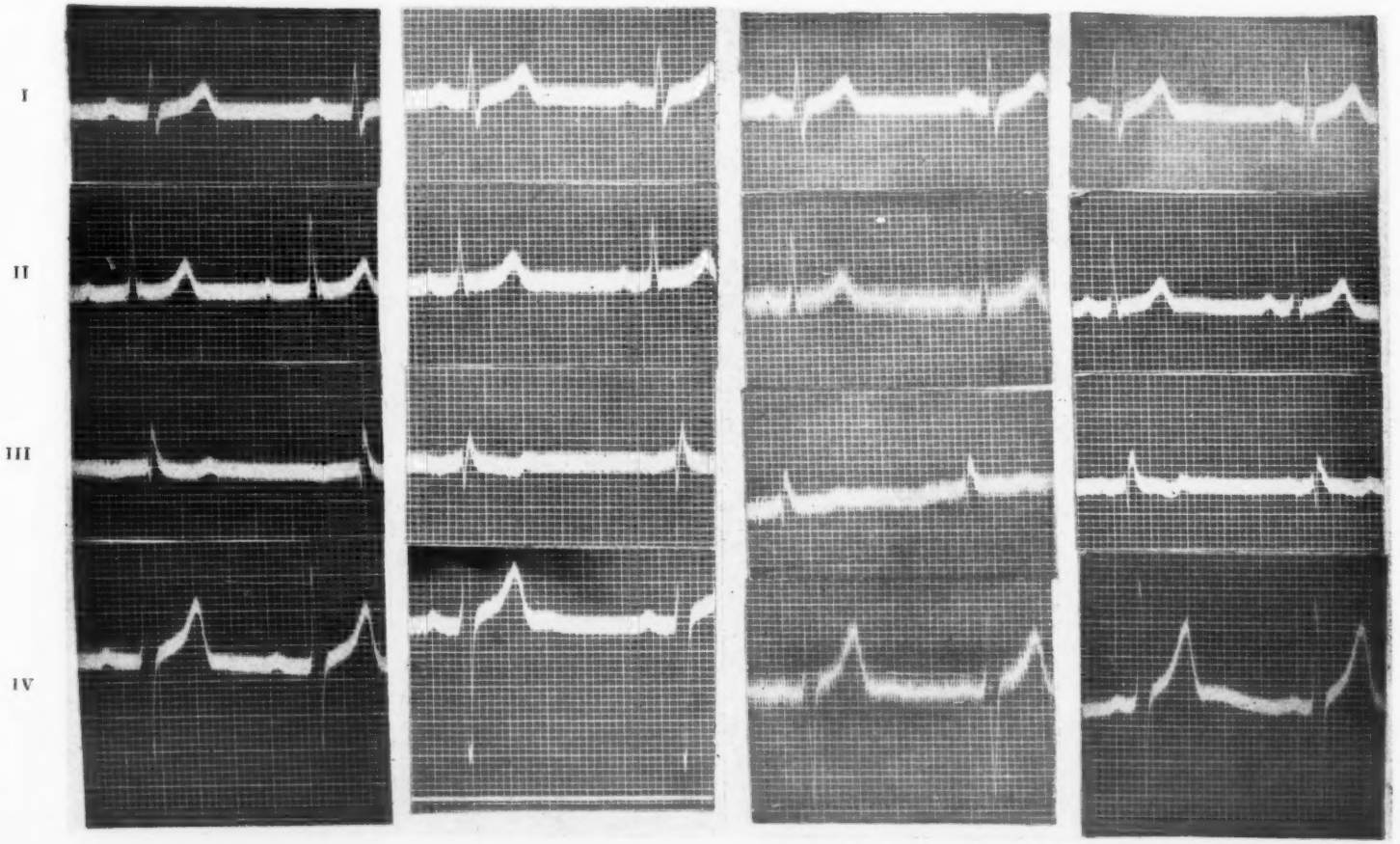


Fig. 1.—Case 1. The P-R intervals progressively lengthened until their duration was 0.26 second. This interval decreased and is seen to be within normal limits in the last two tracings. The S-T segments were slightly depressed in the earlier tracings. They returned to normal in the later tracings. Illustration continued on opposite page.

Fig. 1.—Case 1. The P-R intervals progressively lengthened until their duration was 0.26 second. This interval decreased and is seen to be within normal limits in the last two tracings. The S-T segments were slightly depressed in the earlier tracings. They returned to normal in the later tracings. Illustration continued on opposite page.



2/14/45
P-R Interval, 0.24

2/19/45
P-R Interval, 0.20

2/23/45
P-R Interval, 0.16

3/5/45
P-R Interval, 0.16

Fig. 1 (Cont'd).—*For legend, see opposite page.*

On admission, the patient was acutely ill and had considerable pain. The temperature was 101°, F., the pulse rate was 90, and the respirations were 20 per minute. The tonsils were large and chronically infected. The heart was of normal size, with sounds of poor quality, an apical gallop rhythm, and a soft, blowing, apical, systolic murmur which was not transmitted. The right wrist and both knees were swollen, red, and hot. The spleen was not palpable. Over the lower legs there was a macular, reddish, discrete, petechial rash, most dense about the ankles and knees. Initial laboratory studies showed: red blood cells, 3,600,000; a moderate leucocytosis; an elevated sedimentation rate of 26 mm. in one hour; and albumin, white blood cells, red blood cells, and coarse and finely granular casts in the urine. A prothrombin determination, a platelet count, and a blood culture were normal. An electrocardiogram (Fig. 1) taken on admission was normal, but serial electrocardiograms for the next five days revealed progressive increase of the P-R interval from 0.16 second to a maximum duration of 0.26 second on the sixth hospital day. Depression of the S-T segments occurred and was considered to be suggestive of ventricular myocardial damage. An x-ray film of the chest and heart was normal.

The diagnosis of acute rheumatic fever with purpuric manifestations, associated with acute nephritis, was made, and the patient was given sodium salicylate. The prothrombin time determinations, although diminished, remained within normal limits.

Four days after admission the rash had practically disappeared, and after seven days there remained only a faint pinkish-brown discoloration. The temperature and pulse rate became normal within seven days, and the joint symptoms rapidly subsided. The apical systolic murmur persisted but did not increase in intensity, and the heart sounds became normal. Seven days after admission the P-R interval had decreased to 0.24 second; five days later it was normal and remained so during the remainder of hospitalization. The sedimentation rate remained elevated and repeated urinalyses continued to show evidence of acute nephritis.

Six weeks after admission the sedimentation rate and all other studies were normal except urinalysis, which continued to show a trace of albumin. Salicylate therapy was discontinued. Two months after admission the patient was allowed out of bed and during the next month his activities were gradually increased; during this time all studies remained normal.

CASE 2.—J. L., a 19-year-old Seaman, First Class, was admitted to the hospital on Feb. 7, 1945. For one week prior to admission the patient had had a slight cold and sore throat, for which he received no medication. The day prior to admission he noted the onset of a painful swelling of the left knee and ankle, followed rapidly by the same symptoms in the right knee, then by the appearance of a rash about the ankles which spread quickly to cover the entire lower legs. The past, occupational and family histories were negative concerning rheumatic fever, allergy, or exposure to toxic agents.

On admission the patient was acutely ill and had severe joint pains. The temperature was 99° F., the pulse rate was 94, and respirations were 16 per minute. The heart was normal in size, its sounds were normal, and a soft systolic murmur was audible over the pulmonic area. The spleen was not palpable. There was local heat, swelling, pain on motion, and tenderness of the left knee and both ankles. Over both lower legs there was a deep red, macular, splotchy rash, in areas so extensive as to appear confluent (Fig 2).

Initial laboratory studies revealed: red blood cells, 3,900,000; a slight leucocytosis with a normal differential count; elevation of the sedimentation rate to 25 mm. in one hour; and a prothrombin determination 80 per cent of normal. Urinalysis, a blood culture, and a platelet count were normal.

An electrocardiogram taken on the second hospital day revealed a pronounced sinus arrhythmia with a bradycardia, a varying P-R interval, and ventricular escape. Two days later the electrocardiogram showed no significant change except a decreased nodal irritability. On the fourth hospital day the electrocardiogram returned to normal and remained so throughout hospitalization (Fig. 3). An x-ray film of the lungs and heart was normal.

On the second hospital day the temperature rose to 102° F. and there was an exacerbation of the migratory polyarthritis involving the right elbow and wrist.

A tentative diagnosis of acute rheumatic fever with purpuric manifestations was made, and the patient was placed on sodium salicylate therapy. During this time the results of the pro-

thrombin determinations declined but remained within normal limits. Four days after admission the temperature and pulse were normal, the joint symptoms had disappeared, and the rash had faded considerably. The sedimentation rate remained elevated but all other laboratory procedures were normal. The sedimentation rate became normal five weeks after admission. The patient was then allowed out of bed and salicylate therapy was discontinued. During the next month, all studies remained normal, there were no further symptoms or complaints, and the patient's activities were gradually increased.

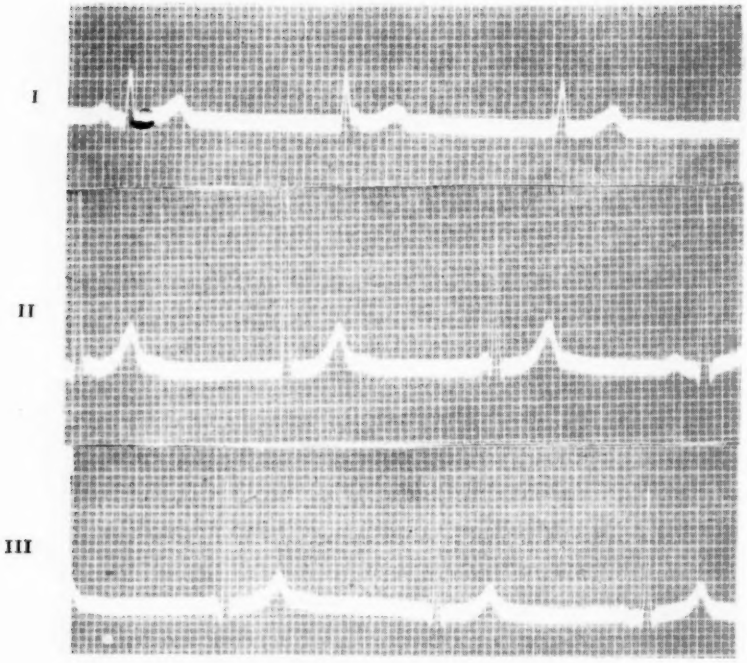
Fig. 2.—Case 2. The rash at the height of the illness was macular in type and deep red in color. It was present over both lower legs and so extensive that it appeared to be confluent.

CASE 3.—F. B., an 18-year-old Seaman, Second Class, was admitted to the hospital on Feb. 25, 1945. Two weeks previously he had had a mild upper respiratory infection for which he was given fifteen sulfadiazine tablets. Two days before admission a rash appeared over both lower legs and spread rapidly during the next thirty-six hours to involve the entire lower extremities. Except for mild soreness associated with the rash, the patient had no complaints. The past, occupational, and family histories were negative for rheumatic fever, allergy, or exposure to toxic agents.

On admission the patient was found to be well developed and well nourished and in no distress. The temperature was 99.8° F., the pulse rate was 100, and the respirations were 20 per minute. The throat appeared normal. No abnormality of the heart was apparent. The spleen was not palpable. Over the lower extremities there was a diffuse, dark, wine-red, macular, mottled rash, in places so extensive as to be confluent (Fig. 4).

Initial laboratory studies revealed: moderate anemia; red blood cells, 3,300,000; slight leucocytosis with a normal differential count; an elevated sedimentation rate of 27 mm. in one hour; a prothrombin determination of 72 per cent of the normal; and a normal platelet count. A blood culture taken on admission was negative. Electrocardiograms on three occasions were normal. Urinalysis revealed only a trace of albumin.

The exanthem rapidly subsided after two days, but the patient continued to have a low-grade fever. Urinalysis showed evidence of nephritis with albumin, red and white blood cells, and casts. The persistent urinary findings were consistent with a clinical diagnosis of acute glomerulonephritis.



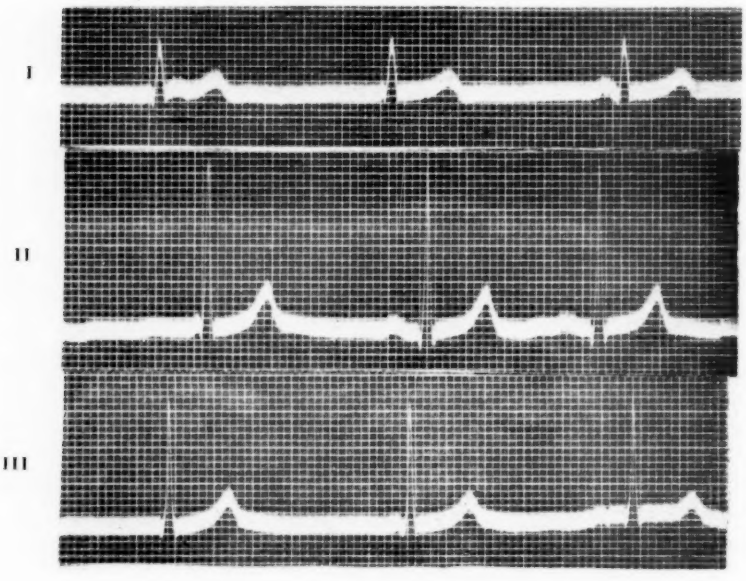


Fig. 3.—Case 2. The electrocardiogram on the second hospital day, Feb. 8, 1945, showed a sinus bradycardia and sinus arrhythmia with ventricular escape. The tracing made Feb. 9, 1945, shows essentially the same findings. Tracings made on and after Feb. 10, 1945, were normal. Illustration continued on opposite page.

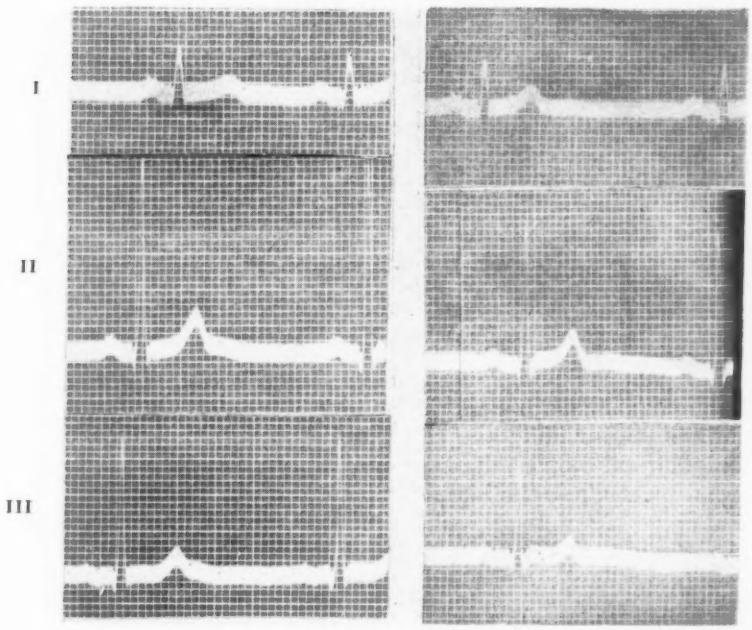


Fig. 3 (Cont'd).—*For legend, see opposite page.*

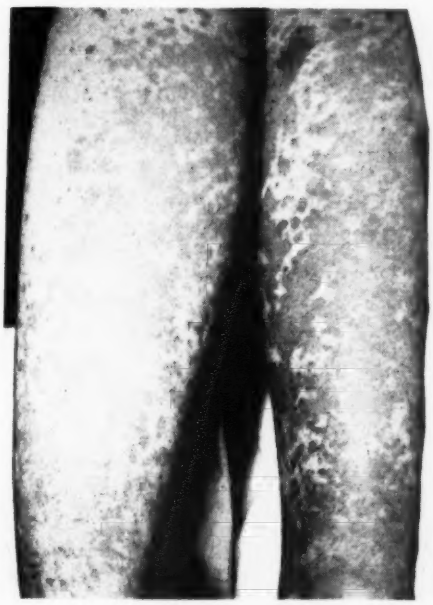


Fig. 4.—Case 3. On admission to the hospital, there was a dark wine-red, macular rash over both lower extremities. The rash was extensive and in places confluent.

On the eighth hospital day the patient began to have transitory pains in both knees and the right elbow of twenty-four hour's duration without any positive physical findings. Otherwise there were no rheumatic manifestations.

Two months after admission the patient had no complaints and physical examination was completely negative, but the sedimentation rate continued elevated and the urinary findings continued to show evidence of nephritis.

DISCUSSION

The clinical association of rheumatic fever with cutaneous nodules and erythematous and hemorrhagic eruptions has been recognized for many years. Wells[1] and then Bright[1] in 1831 recorded instances of an exanthem in rheumatic fever and credit has been given to Rayer[2] for being the first to describe the association of erythema multiforme with acute rheumatic fever in 1835. Among the more prominent cutaneous manifestations of acute rheumatic fever are the following:

a. The rheumatic erythemas including erythema multiforme, erythema annulare, and erythema marginatum. Of these, erythema multiforme is by far the most prevalent.
b. Hemorrhagic eruptions including purpura. This group is distinct from purpura rheumatica or Schöenlien's purpura in which the association with rheumatic fever is uncertain.
c. Subcutaneous nodules.
d. Erythema nodosum.

Although the estimated incidence of cutaneous manifestations in rheumatic fever has varied from 4 per cent to over 75 per cent, the impression prevails that this condition is infrequent. In a review of rheumatic fever for 1941, Hench[3] stated that 5 per cent of the cases demonstrated skin lesions. Keil,[4] in a summary of 523 cases of acute rheumatic fever, found that 10 per cent had erythematous lesions. Swift[5] mentions the occurrence of various skin manifestations. White[6] states that this condition may occur in from 2 per cent to 75 per cent of patients with rheumatic fever, the percentage varying in different groups and in different parts of the world. According to this author erythema multiforme is the commonest of the skin lesions and occurs at some period in 15 per cent of all cases of acute rheumatic fever. In this hospital over the past six months there have been sixty-three admissions for acute rheumatic fever, of which three, or 4.7 per cent, demonstrated cutaneous lesions.

Thus, the general incidence of rheumatic cutaneous lesions is low and the specific appearance of purpura as a skin manifestation is even more rare. Hansen[7] refers to purpura as being a cause of mistaken diagnosis in only one case in a review of 167 patients with rheumatic fever; and in a further review of 271 cases he mentions purpura as a rare possible source of confusion in the initial diagnosis of rheumatic fever. Both White and Swift refer to purpuric manifestations as occasionally seen. Lichtwitz[9] mentions purpura as occurring in rheu-

matic fever and considers it a systemic disorder centering in the capillaries which is less severe and distinct from the so-called Henoch's purpura sometimes seen in other infectious conditions.

Purpura, associated with acute glomerular nephritis, appears even more infrequently. Minot[10] mentions purpura as being very rarely associated with chronic nephritis. Fishberg,[11] in discussing acute glomerulonephritis, states that purpuric spots occasionally appear in small numbers.

The relationship between acute rheumatic fever and acute nephritis has received extensive study in the past few years. It is felt that generalized involvement of the vascular system is a common accompaniment, if not a constant manifestation, of the rheumatic process. The most common pathologic finding in rheumatic fever has been described as a nonsuppurating, perivascular infiltration, affecting chiefly the smaller vessels, associated with edema and round cell infiltration, and leading to the formation of new connective tissue. Although these changes are most frequently found in the myocardium and endocardium, they have been described as affecting the coronary arteries as well as the renal vessels.

It is well recognized that acute glomerulonephritis in association with acute rheumatic fever is very rare. Hutton and Brown[12] state that in large groups of patients who have acute rheumatic fever, nephritic complications vary from 0.67 to 7 per cent. These authors described four cases of rheumatic fever with clinical evidence of nephritis, in which a typical rheumatic endarteritis, associated with characteristic Aschoff bodies, was demonstrated at autopsy in both the myocardium and kidneys. Blaisdell,[13] in a review of sixteen autopsied patients with rheumatic fever, found typical perivascular infiltration present in the kidneys in fourteen cases. The primary lesions were in the interstitial tissues and the degenerative hyaline changes observed in the glomeruli were felt to be nutritional disturbances secondary to the interstitial vascular changes. Blaisdell[13] felt that "while the changes noted are of most frequent occurrence and give rise to a definite interstitial nephritis, the renal damage is only occasionally of sufficient degree to lead to a diagnosis of kidney disease during life."

From the literature it can be accepted that acute rheumatic fever is a disease resulting in widespread pathologic changes. It well may be that the purpuric lesions are themselves a part of this generalized process. Deterioration of the capillary wall, with red blood cells escaping through these capillary defects, is considered to be the underlying cause in this type of purpura. The associated renal lesions and, at rare intervals, the clinical evidence of nephritis, lends further evidence of the generalized nature of the rheumatic infection. It is noteworthy that while acute glomerulonephritis associated with rheumatic fever, even subclinically, is rare, renal lesions of an interstitial nature are observed relatively frequently, although, here again, clinical manifestations are unusual. The high incidence of cardiac involvement and the occasional presence of skin lesions may perhaps be evidence of a similar generalized pathologic process in acute glomerulonephritis. It is of interest and importance that skin lesions or pur-

pura can be an initial symptom of these two maladies, and this fact should emphasize the necessity of searching for the underlying pathogenesis in patients admitted to the hospital with this symtomatic diagnosis.

SUMMARY

1. Three cases of symptomatic purpura have been presented. In two of these the underlying factor was considered to be acute rheumatic fever, in one of which there was evidence of simultaneous nephritis. The primary cause in the third case was acute glomerulonephritis.

2. The various cutaneous manifestations of acute rheumatic fever and acute glomerulonephritis have been outlined.

3. The nephritic manifestations of rheumatic fever have been discussed together with the relationship between these two conditions.

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Abstracts and Reviews

Herrmann, G. R.: Blood Plasma Proteins in Patients With Heart Failure. Ann. Int. Med. **24**:893 (May), 1946.

This report is an analysis of blood protein estimations before and after dissipation of the edema in 100 patients with congestive heart failure. The results showed slight but definitely subnormal albumin values with slight compensatory increases in globulin values during the edematous stage. After the dissipation of the edema, the blood proteins did not immediately rise to normal levels, but there were gradual accretions. It is suggested that this lag is due to the fact that the liver cannot assist with protein anabolism until circulatory equilibrium is re-established. The lowest blood protein levels were noted in patients who had suffered congestive failure for many months.

WENDKOS.

Anderson, D. P., Allen, W. J., Barcroft, H., Edholm, O. G., and Manning, G. W.: Circulatory Changes During Fainting and Coma Caused by Oxygen Lack. J. Physiol. **104**:426 (April), 1946.

Healthy male subjects, aged twenty to thirty years, reclining with the back supported at an angle of about 45 degrees, breathed oxygen-nitrogen mixtures containing approximately 10, 8, 7, and 6 per cent oxygen. The pulse rate, arterial blood pressure, and forearm blood flow (plethysmographic) were recorded. Among thirteen subjects, there were three fainters and ten nonfainters. A typical test in a fainter consisted of an initial rise in pulse rate, systolic arterial pressure, and a slight increase in forearm blood flow followed by vasovagal syncope, during which both the systolic and diastolic pressures and the pulse rate fell below control levels. Nonfainters, however, lost consciousness without showing any signs of the vasovagal reaction and maintained their tachycardia and elevated systolic pressure for the duration of the hypoxic period. In both the fainters and nonfainters forearm blood flow rose to significantly high levels.

In the same group of subjects hypoxia was superimposed upon a simulated hemorrhagic state induced by trapping blood in the lower extremities by means of venous tourniquets. In this "posthemorrhagic" hypoxia a much higher percentage of vasovagal syncope was encountered: ten of the thirteen subjects fainted. The circulatory reactions in this group of experiments were, on the whole, the same as those observed in vasovagal syncope caused by simple hypoxia.

The increase in forearm blood flow in vasovagal syncope and in coma due to hypoxia is considered to be due to vasodilation in skeletal muscle.

It is suggested that wounded men who have lost significant quantities of blood may need oxygen in an atmosphere of low oxygen tension.

FRIEDLAND.

Levy, L., and McKrill, N.: Results in the Treatment of Subacute Bacterial Endocarditis. Arch. Int. Med. **77**:367 (April), 1946.

These authors present a rather complete review of the literature relating to the therapy of subacute bacterial endocarditis in the past, and record the results of their own treatment in eleven patients. Their plan of treatment consisted of the administration of 200,000 units of penicillin intramuscularly in divided doses every two hours. Sulfadiazine, in a dosage of 1 Gm. every four hours day and night, was also administered with the penicillin. Nine patients received heparin dissolved in 1,000 c.c. of a 5 per cent solution of dextrose in distilled water

as a continuous intravenous drip. The amount of heparin given was that required to maintain a clotting time of between thirty to sixty minutes; in twenty-four hours, this varied between 90 to 300 mg. (9 to 30 c.c.). During heparinization, frequent reactions were observed. These consisted of fever, sometimes with a temperature up to 108° F., chills, mild excitement, and some disorientation. Some of these reactions were believed to be due to the release of protein from the decomposition of bacteria, some to heparin sensitivity, some to embolic phenomena, and some were not explainable. Of the eleven patients, seven were considered to be probably cured; one died from a heparin reaction, and three failed to recover. As a result of autopsy in four cases, they conclude that heparinization favors fragmentation of the vegetation leading to embolism, and that large cerebral hemorrhages are due to bleeding into infarcted areas as a result of the diminished coagulability of the blood. As a result, they advise heparinization only in a few selected cases.

After the patient recovers from an episode of subacute bacterial endocarditis, they suggest frequent follow-up examinations and elimination of foci of infection. BELI ET.

McIntosh, Berkeley C., and Jackson, Robert L.: Angles of Clearance: A Method for Measuring the Cardiac Size of Children With Rheumatic Heart Disease (A Comparison With the Cardiothoracic Index). Am. J. Dis. Child. 71:357 (April), 1946.

The use of the angle of clearance as a fluoroscopic method for measuring cardiac size was devised by Wilson in 1934. After comparing it with other methods of measuring the size of the heart of patients with rheumatic heart disease, she concluded that the angle of clearance differentiated the normal from the abnormal with greater frequency.

Jackson studied this angle and its reliability as a measurement of cardiac size in 1943 and established normal values for children using a modified technique. The most significant changes were the measurement of two angles instead of one and the designation of these as the first and second angles of clearance. The first angle is that at which the left dorsal border of the heart separates from the transverse process of the vertebrae and the second is that at which the left dorsal border of the heart clears the anterior surface of the vertebral bodies. Wilson had originally established the upper limit of normal for this second angle as 55 degrees. Jackson found the mean value for the first angle to be 51.8 degrees and for the second angle, 63.2 degrees. The standard deviations were 5.8 and 7.4, respectively. Sixty-one patients with inactive rheumatic heart disease and sixteen with active disease are the basis for this report. Comparison was made with the heart sizes obtained by using the cardiac thoracic diameter and physical examination.

Of the entire group of seventy-seven subjects, 68 per cent showed a second angle of clearance above the selected high normal limit of 70 degrees. Forty-one per cent were above the high normal of 57 degrees as measured by the first angle. Thus the second angle of clearance indicated enlargement in a higher percentage of cases than did the first angle. The cardio-thoracic angle was above normal in only 35 per cent of children. However, if the group of children with a considerable degree of enlargement are eliminated, this difference became even greater and in this group the percentages for the two angles are 41 per cent and 12 per cent, respectively. The cardio-thoracic ratio detected enlargement in none of these cases.

The angles of clearance are capable of showing lesser degrees of cardiac enlargement than is the cardio-thoracic diameter and are a valuable adjunct in detecting changes in heart size caused by rheumatic fever. However, the trends of both are parallel in any given subject and both are of value in following an individual subject. HAUB.

Cristie, R. V.: Penicillin in Subacute Bacterial Endocarditis: Report to the Medical Research Council of 147 Patients Treated in 14 Centers Appointed by the Penicillin Clinical Trials Committee. Brit. M. J. 1:381 (March 16), 1946.

This report covers an eighteen-month period. Fifty-five per cent of the patients were "cured," at least for the duration of the four- to eight-month observation period. There were fifty deaths (34 per cent); in the remaining 11 per cent, the final outcome could not be stated with certainty. A streptococcus was the infecting agent in all cases but one; the majority of cases was found to be infected by *Streptococcus viridans*. Penicillin was administered every three hours intramuscularly or as a continous intramuscular drip with about equal success.

By increasing the period of treatment, using the same total dose (5,000,000 Oxford units), the results improved steadily. With five-day courses, no cures and 70 per cent relapses occurred. Twenty-day courses cured 50 per cent, with a relapse rate of 21 per cent: figures almost twice as high as the percentages obtained with ten-day courses. The best results were obtained with a total dosage of 14,000,000 units in twenty-eight day courses: 61 per cent appeared "cured" during the follow-up period, and no relapses were observed. The duration of treatment was thus the most important factor, but the size of the dose was also important; large doses were more effective. The death rate was relatively constant for each of the groups, ranging between 17 and 40 per cent, with an average of 30 per cent. Relapses usually occurred within thirty days and almost always within fifty days of cessation of therapy. Short, inadequate courses did not prejudice later results with full doses. Although the many relapses were usually early (within a week) the re-treated patients met the averages obtained for the series. Those who did poorly with adequate dosage, though their relapses were longer in appearing, also did poorly when their courses were repeated. A relapse after a twenty-eight day course was serious and justified a six- to eight-week re-treatment period, for the recovery rate was statistically only one-half that of the average obtained for the series. The reason for this was apparently not in the increased resistance of the organism, since this could be demonstrated in only a small minority and was never great. It was concluded that these patients therefore represented a selected group which had a poor response to antibiotic therapy.

In vitro resistance, expressed as multiples of the resistance of the standard Oxford Staphylococcus, was of clinical value only if very great.

Clinical results were as good with "resistant" organisms (compared with the Oxford Staphylococcus) as with "sensitive" strains. Of three patients who had strains more than thirty-two times as resistant as the Oxford Staphylococcus, two died of overwhelming infection. The third patient recovered on a twenty-one day course of 5,000,000 units every twenty-four hours.

Observations on the importance of removing foci of infection and the role of congestive heart failure in the causation of the majority of the deaths were in agreement with reports in current American literature. It was concluded that although excellent results would occur occasionally with any system of dosage lasting for more than ten days, relapses would be unnecessarily frequent unless 5,000,000 units were given for twenty-eight days as routine therapy in all proved cases.

SAŸEN.

Jensen, C. R.: Non-Suppurative Post-Streptococcic (Rheumatic) Pneumonitis. Arch. Int. Med. 77:237 (March), 1946.

The author points out that clinical recognition of the pulmonary lesions in rheumatic fever is increasing, but confusion still occurs in the differential diagnosis of this type of pneumonitis. Jensen presents the clinical-pathological findings in a 19-year-old male who died thirty days after the onset of an initial attack of rheumatic fever, featured at first by typical scarlet fever and soon followed by arthritis, nephritis, and pneumonitis. An apparently satisfactory convalescence from scarlet fever was interrupted on the fifteenth day by polyarthritis, dyspnea, hemorrhagic nephritis, and acute hypertension. Under salicylate therapy, the arthritis subsided and the azotemia was reduced. Dyspnea, however, was increased and eventually was accompanied by cyanosis. An electrocardiogram was normal. Râles were audible throughout both lungs. The patient died in great respiratory distress exactly thirty days after the appearance of a streptococcic pharyngitis and fifteen days after the onset of rheumatic pain.

Post-mortem examination showed large lungs, only slightly crepitant, quite solid and plum purple in many areas but not hard and friable. Microscopy revealed monocytic infiltrations in the alveolar walls, consisting of swollen endothelial cells, large mononuclear type lymphocytes, and plasma cells. Some small but dense collections of these cells were noted, but a true Aschoff body was not found. Special stains were negative for organisms. The alveoli contained edema fluid, many erythrocytes, desquamated alveolar cells, monocytes and a generally sparse infiltration of polymorphonuclears.

The kidneys showed focal interstitial hemorrhage and perivascular lymphocytic and plasma cell collections. Many tubules contained blood, but the glomeruli were rather bloodless.

The heart, which was normal grossly, showed small pericardial and also endocardial collections of lymphocytes and plasma cells histologically.

The author emphasizes the unusual opportunity that was presented in this case to study the pulmonary lesions of rheumatic fever uncomplicated by secondary infection or by changes secondary to heart disease. He describes rheumatic pneumonitis as a non-suppurative tissue reaction similar to that seen in other organs following hemolytic streptococcic infection of the upper respiratory tract; in some instances it was so pronounced as to dominate the clinical picture. Jensen points out the possibility of error in diagnosing such a pulmonary involvement as a virus pneumonitis. He recommends more extensive use of the cold pressor and of the antistreptolysin tests in differential diagnosis. GOULEY.

Hicks, A. M., Painton, J. F., and Hantman, S.: A Clinical Analysis of Primary Atypical Pneumonia, With a Discussion of the Electrocardiographic Findings. Ann. Int. Med. **24**:775 (May), 1946.

This report is based upon an analysis of 321 cases of atypical pneumonia studied in one of the military hospitals in this country during the recent war. Correlations were established between the incidence of the disease and the age, race, weight, length of service, and the season of the year. The clinical features and laboratory findings were reviewed, and the conclusions reached were found to be similar to those expressed in previous reports concerning atypical pneumonia. The same statement was true of the roentgen patterns and the authors' comments concerning treatment of this disease. Electrocardiographic examinations were employed extensively in sixty-three cases, and twelve of this group showed "electrocardiographic evidence suggestive of myocardial and pericardial involvement." Only two of these patients presented clinical evidence suggestive of cardiac abnormality. The changes consisted of RS-T segment elevations, T-wave inversion, a disturbance of A-V conduction, or combinations of these. In seven of the cases there was electrocardiographic reversal to normal, whereas the other five showed irreversible changes which persisted throughout a three-month period of observation. None of the cases came to autopsy. WENDKOS.

Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Austin, R. S.: Beriberi Heart Disease. J. A. M. A. **131**:717 (June 29), 1946.

These authors report their study of a series of twelve cases which were diagnosed as beriberi heart disease from 1940 to 1945. Five patients died in the hospital; autopsies were performed on three patients. The authors believe that the oriental concept of beriberi heart disease as characterized by Wenckebach criteria probably has hindered the diagnosis in many instances. This is particularly true in the large group of cases of beriberi heart disease which do not manifest the rapid circulation and which closely resemble other types of degenerative heart disease. The requirements for diagnosis in their series were (1) insufficient evidence of other etiology; (2) three or more months on a thiamine-deficient diet; (3) signs of neuritis or pellagra; (4) enlarged heart with sinus rhythm; (5) dependent edema; (6) elevated venous pressure; (7) minor electrocardiographic changes; (8) recovery with decrease in heart size; or (9) autopsy findings consistent with beriberi heart disease. The chief factor in diagnosis includes the realization that the etiologic nature of the heart disease is obscure. The differential diagnosis includes coronary arteriosclerosis, Fiedler's myocarditis, and idiopathic hypertrophy.

Alcoholism accounted for the poor dietaries of eleven patients. The majority of diets were deficient not only in thiamine, but also in the other water-soluble vitamins, particularly niacin, riboflavin, and ascorbic acid. Although the time interval required to produce the degree of hypovitaminosis sufficient to produce cardiac abnormalities varies considerably in different individuals, ninety days is the arbitrary point selected. In all twelve cases there was other clinical evidence of nutritive failure. There was always some indication of peripheral neuritis or pellagra. In six cases evidence of both disorders was found. Eight of the twelve patients had anemia, which in three instances was normocytic and in five macrocytic in type. Hypoproteinemia was con-

sistently observed in these patients. Ten of the patients during life showed clinical and roentgenologic evidence of cardiac enlargement. Dependent edema was present in eleven of the twelve patients, and elevated venous pressure was observed in nine. Serial electrocardiograms were made in ten of the twelve cases and all showed abnormalities. The most common abnormalities observed were low voltage and minor alterations in the T waves.

When beriberi heart disease was suspected, the patient was put on a strict regimen which included rest in bed and a diet very low in thiamine. The control period was continued as long as the patient's condition permitted. Large doses of thiamine were then given intravenously. Most cases which showed improvement did so gradually; only one showed dramatic improvement in a period of twenty-four hours. Three of five patients who received digitalis apparently benefited from this drug. There is some uncertainty as to the origin of the dictum that digitalis is of no aid in this condition and that if the heart responds well to this drug the diagnosis of beriberi is eliminated.

While alterations in the myocardium in beriberi heart disease have been described and studied repeatedly for many decades, no pathognomic picture has been revealed. Three of their cases which came to necropsy showed degenerative changes of the heart muscle and interstitial edema. These observations were considered consistent with but not diagnostic of beriberi heart disease. In two instances in which the nervous system was examined, definite lesions in the central, peripheral, and autonomic nervous systems were revealed. BELLET.

Nathanson, M. H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex. Arch. Int. Med. 77:491 (May), 1946.

This report was based on a study of 115 patients showing hyperactive carotid sinus reflexes. The carotid sinus was considered hyperative when it fulfilled the following criteria: (1) a cardiac standstill of at least five seconds; (2) cardiac inhibition induced by simple pressure on the carotid sinus without massage of sinus; (3) standstill of equal intensity elicited on several tests. The youngest patient was 30 and the oldest in the group was 81 years of age; the average age was 58.9 years. Of the 115 patients, seventy-seven (67 per cent) presented no symptoms suggestive of carotid sinus syndrome. In ten cases, manifestations of the carotid sinus syndrome were the chief complaints. Attacks of syncope were experienced by only six patients. Symptoms resembling those of carotid sinus syndrome were presented by fifteen patients, but some mechanism other than the hyperactive carotid sinus reflex could be demonstrated as a basis for the attacks. In five of these patients, there was a true vertigo with nausea and tinnitus, indicative of Ménière's syndrome. The sensations following pressure on the carotid sinus had no similarity to the sensations at the time of the spontaneous attacks. In four patients, the symptoms of faintness and dizziness were associated with attacks of paroxysmal tachycardia.

A definite distinction is made between the hyperactive carotid sinus reflex which designated a hyperactive response to stimulation of the carotid sinus and the carotid sinus syndrome which designated a clinical condition. The author explains the presence of symptoms in some and the absence of symptoms in others with similar degrees of sensitivity to a difference in individual response to cerebral ischemia.

This author also made an attempt to determine the site of the hyperactive cardioinhibitory reflex. Pressure over the carotid sinus was shown by Hering to elicit two independent effects: (1) a cardioinhibitory effect and (2) a vasodepressor effect. The former may be abolished by atropine, permitting observations of the vasodepressor effect. Blood pressure readings were taken during stimulation of the carotid sinus, before and after administration of atropine. It was observed that there was definite lowering of the blood pressure following carotid sinus stimulation in the atropinized patient. He therefore concludes that either the vagus center in the medulla or some portion of the efferent path in the vagus nerve must be considered responsible for the hyperactive response. This observation is of practical importance because denervation of the carotid sinus would not insure a consistent and permanent cure if the hypersensitivity was predominantly in the vagus nerve. BELLET.

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